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# DISEASES OF THE LIVER

## VIII. THE VARIOUS TYPES OF SYPHILIS OF THE LIVER WITH REFERENCE TO TESTS FOR HEPATIC FUNCTION *

PAUL A. O'LEARY, M.D.

CARL H. GREENE, M.D.

AND

LEONARD G. ROWNTREE, M.D.

ROCHESTER, MINN.

The protean nature of syphilis is nowhere better illustrated than by a consideration of its visceral manifestations; in fact, the recognition of visceral syphilis by clinical means alone is often difficult if not impossible. In consequence, great emphasis has been placed on those laboratory procedures which are of assistance in showing the presence of syphilitic infection.

Although serologic tests are of great value in the recognition of visceral syphilis, they do not tell which organ is involved, or the degree of injury produced by the syphilitic process. Such information, on the other hand, would be of inestimable value in diagnosis, prognosis and treatment. Particularly is this true in cases of syphilis of the liver. Additional diagnostic measures are desirable, and the recent interest in tests for hepatic function is evidence of the need for such information.

Recent studies of the physiologic activities of the liver have served to emphasize its manifold functions. Many of them are but imperfectly understood as yet. A test has not been devised for estimating the sum of the various activities of this organ. It is not surprising, then, that there have been great differences of opinion regarding the clinical value of the various proposed tests of hepatic function. We wish to report our experiences with certain of these tests in the study of syphilitic disease of the liver and our observations regarding their behavior in patients without a previous history of disease of the liver, in whom hepatic complications developed following treatment for syphilis.

We have studied more than 100 cases of syphilis complicated by various forms of hepatic disease. In many it has been possible to make repeated studies over periods varying from six months to six years.

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* From the Section on Dermatology and Syphilology and the Division of Medicine, the Mayo Clinic and the Mayo Foundation.

The diagnosis has been made, for the most part, on the basis of clinical impressions and the effect of therapeutic tests. In some cases, laparotomy or necropsy has permitted of a positive pathologic diagnosis.

It is obviously impossible to present so varied a mass of material without careful consideration of the clinical features of the disease as well as of the different laboratory tests. Syphilis of the liver, in its clinical manifestations at least, is not a common complication of syphilis. During the last ten years, 171 patients with various forms of hepatic syphilis have been seen in the Mayo Clinic. This gives an incidence of approximately one in 2,000 medical and surgical admissions. Estimated with relation to syphilis, hepatic complications of one form or another are to be observed in less than 1 per cent of the syphilitic patients in the Mayo Clinic. The incidence of hepatic syphilis is probably greater than these figures indicate, as evidenced by the finding of previously unrecognized syphilitic lesions in the liver at necropsy, and also by the frequency with which dormant hepatic syphilis becomes symptomatic during or following antisyphilitic treatment. McCrae [1] reported an incidence of hepatic syphilis of 0.2 per cent recognized clinically, and 1.5 per cent found at necropsy. It appears that approximately 2 per cent of syphilitic patients under treatment will develop one or more manifestations of hepatic complication. Various estimates of the serologic data show that in approximately 90 per cent of the patients with hepatic syphilis the Wassermann reaction of the blood is positive.

The following classification of syphilitic disease of the liver, modified from that suggested by Stokes,[2] has been used in this study:

Acute Syphilis

1. Hepatitis of acute syphilis (benign)
2. Acute yellow atrophy (severe)

Late Syphilis

1. Asymptomatic
2. Diffuse hepatitis of late syphilis
3. Gummatous hepatitis (hepar lobatum)
4. Chronic hepatitis or syphilitic cirrhosis
   (*a*) Chronic hepatitis with jaundice (biliary cirrhosis)
   (*b*) Chronic hepatitis with ascites (portal cirrhosis)

Hepatic Complications of Treatment for Syphilis

1. Postarsphenamine jaundice (arsenical or infectious)
2. Icterus gravis or acute yellow atrophy of the liver
3. Hepatorecurrence and Herxheimer effect in the liver
4. Treatment cirrhosis
5. Jaundice associated with malarial inoculation

1. McCrae, Thomas: Tertiary Syphilis of the Liver, Am. J. M. Sc. **164**:625, 1912.

2. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926, p. 1144.

In this study we present a record of our personal experience and opinion rather than a detailed discussion of the clinical and pathologic features of these various types of hepatic syphilis. The details must be sought in the writings of Lancereaux,[3] Fournier,[4] Osler,[5] Hutchinson,[6] Rolleston,[7] McCrae,[8] Stokes,[2] Wile [9] and others. Instead, we present a summary of the essential clinical features of the different conditions, together with abstracts of the histories of illustrative cases. The complete laboratory data are given in the accompanying tables.

This study was started six years ago, and the majority of the tests considered of value in estimating hepatic function since that time have been utilized. In the beginning, emphasis was placed on the fructose tolerance test, the nitrogen partition in the blood, the determination of the serum bilirubin content and the phenoltetrachlorphthalein test. Later, the bromsulphalein test and the determination of the bile acids in the blood were added. The technic of these various tests already has been reported in [10] detail [11] although we have slightly modified the bromsulphalein test. Rosenthal and White [12] recommended the injection of 2 mg. of bromsulphalein to each kilogram of body weight. We have found a dose of 5 mg. for each kilogram more satisfactory in routine use. Succeeding blood samples are then taken fifteen, thirty and sixty minutes after the injection of the dye. A positive Wassermann reaction, the Kolmer technic being used, was obtained in either the blood or the spinal fluid in all cases included in the study. In consequence, specific notation of this test has been omitted from the tables.

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3. Lancereaux, Etienne: A Treatise on Syphilis, Historical and Practical, London, New Sydenham Society, 1868-1869.

4. Fournier, Jean-Alfred: The Treatment of Syphilis, New York, Rebman Company, 1906, p. 219.

5. Osler, William; Churchman, J. W., and Conner, L. A.: Syphilis, in Osler, William; and McCrae, Thomas: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1925, p. 389. Osler, William, and Gibson, A. G.: Visceral Syphilis, in D'Arcy, Power; and Murphy, J. K.: A System of Syphilis, London, Oxford University Press, 1914, vol. 3, p. 1.

6. Hutchinson, Jonathan: Syphilis, London, Cassell & Company, 1901, p. 532.

7. Rolleston, H. D., and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 884.

8. McCrae, Thomas, and Caven, W. R.: Tertiary Syphilis of the Liver, Tr. A. Am. Phys. **41**:168, 1926.

9. Wile, U. J.: Syphilis of the Liver, Arch. Dermat. & Syph. **1**:139 (Feb.) 1920.

10. Greene, C. H.; Snell, A. M., and Walters, Waltman: Diseases of the Liver: I. A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925.

11. Aldrich, Martha, and Bledsoe, Mary Sue: Studies in the Metabolism of the Bile: I. A Quantitative Pettenkofer Test Applicable to the Determination of Bile Acids in the Blood, J. Biol. Chem. **77**:519, 1928.

12. Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 14) 1925.

### SYPHILIS WITHOUT APPARENT INVOLVEMENT OF THE LIVER

In the course of this study we tried the various tests for hepatic function in a number of patients with syphilis in whom there was no involvement of the liver. Many of these patients had late syphilis of the central nervous system or of the cardiovascular system. They did not present symptoms referable to the liver, and there was no enlargement or other evidence of hepatic involvement. In a few, exploratory laparotomy had been performed, at which time the liver appeared to be normal. This series served as a control, and normal results were obtained throughout (table 1). The serum bilirubin content varied between 0.1 and 1.5 mg., and an indirect van den Bergh reaction was obtained. The phenoltetrachlorphthalein reading varied between 3 and 9 per cent in the one hour sample, and the bromsulphalein between 0 and 8 per cent in the half hour sample. The Pettenkofer reaction gave a value for the bile acids between 4 and 5.2 mg. These values correspond well with the usually accepted range for the normal.

### HEPATITIS OF ACUTE SYPHILIS

The diffuse hepatitis of acute syphilis is a rare complication of the disease. Wile and Karshner,[13] who reviewed this subject, called attention to the fact that it appears in two forms: the mild type associated with jaundice, malaise and enlarged liver appearing simultaneously with the secondary eruptions, and the severe type which, as a rule, progresses to acute yellow atrophy and death. The presence of the clinical evidence of acute syphilis, together with jaundice and its attendant symptoms, lead to the presumptive diagnosis. We are able to report the case of a patient in whom a moderate degree of hepatitis developed in connection with the appearance of mucous patches and a maculopapular syphilid and in whom the jaundice promptly disappeared following judicious antisyphilitic treatment.

Case 31 (table 2).—A hair-dresser, aged 21, acquired a chancre in November, 1927. Four weeks later, a florid, papular, secondary eruption developed. Jaundice appeared a few days later. She came to the clinic on Dec. 28, 1927, three weeks after the onset of the jaundice.

At the time of examination the patient had an acute, papular, secondary rash and mucous patches (condyloma latum). A dark-field examination of the lesions was positive for the *Spirochaeta pallida*. The Kolmer modification of the Wassermann reaction on the blood also was positive and was graded 44.[14] There

13. Wile, U. J., and Karshner, R. G.: Icterus Gravis Syphiliticus: Its Relation to Acute Yellow Atrophy, J. A. M. A. **68**:1311 (May 15) 1917.

14. By this method of grading is indicated the result of a set-up of three tubes, of which the third is a control and the first two are read. The result "44" means that in the first tube, which contained 0.1 cc. of patient's serum, and also in the second tube, which contained 0.05 cc. of patient's serum, the result was ++++.

TABLE 1.—*Syphilis Without Apparent Involvement of the Liver*

PART 1

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice | Blood Nitrogen Partition, Mg. for Each 100 Cc. | | | | | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Phenoltetrachlorphthalein Test | | | | Fructose Tolerance Test | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Non-protein Nitrogen | Urea | Uric Acid | Creatinine | Amino-Acid Nitrogen | | | Dye in Serum, per Cent | | | Dye in Urine, Mg. | | |
| | | | | | | | | | | | | | 15 Min. | 1 Hour | 2 Hours | | | |
| 1 | 11/12/24 | 37 | M | 0 | 0 | 31 | 27 | 3.5 | 1.3 | 6.6 | 0.7 | 0 | 13 | 9 | 3 | 0.0 | .. | Neurosyphilis |
| 2 | 8/25/25 | 53 | M | 0 | 0 | .. | 42 | .... | .... | .... | 1.4 | 0 | 10 | 8 | 5 | .... | .. | Neurosyphilis |
| 3 | 10/ 9/25 | 40 | F | + | 0 | .. | .. | .... | .... | .... | 1.5 | 0 | 10 | 3 | 1 | .... | .. | Neurosyphilis |
| 4 | 8/18/25 | 43 | F | 0 | 0 | .. | 26 | .... | .... | .... | 0.2 | 0 | 8 | 3 | 0 | .... | .. | Neurosyphilis |
| 5 | 9/ 9/24 | 52 | M | 0 | 0 | 40 | 46 | 3.0 | 1.7 | 6.8 | 0.6 | 0 | 8 | 4 | 2 | 0.2 | .. | Latent syphilis |
| | 9/30/24 | .. | .. | .. | .. | 33 | 27 | 2.2 | 1.5 | 5.4 | 0.6 | 0 | 7 | 3 | 0 | 0.0 | .. | |
| 6 | 6/30/24 | 38 | M | 0 | 0 | 34 | 33 | 3.3 | 1.4 | 6.4 | 0.9 | 0 | 7 | 4 | 1 | 0.0 | .. | Neurosyphilis |
| 7 | 6/18/24 | 42 | M | 0 | 0 | 33 | 10 | 2.6 | 1.6 | 5.6 | 0.7 | 0 | .. | 3 | 2 | 0.4 | .. | Paresis; neurosyphilis |
| | 7/ 8/24 | .. | .. | 0 | 0 | 40 | 40 | 2.7 | 1.6 | 7.0 | 0.7 | 0 | 7 | 4 | 2 | 0.2 | .. | |
| 8 | 10/22/24 | 39 | F | 2 | 0 | 26 | 21 | 2.2 | 1.4 | 6.3 | 1.1 | 0 | 6 | 3 | 2 | 0.6 | .. | Neurosyphilis |
| 9 | 6/24/24 | 20 | F | 0 | .. | 40 | 34 | 3.9 | 1.5 | 6.1 | 0.6 | 0 | 7 | 3 | 0 | .... | .. | Acute syphilis |
| 10 | 7/28/24 | 47 | F | 0 | 0 | 35 | 48 | 3.5 | 1.3 | 6.9 | 1.0 | 0 | 6 | 3 | 1 | .... | .. | Neurosyphilis |
| 11 | 3/25/25 | 37 | M | + | 0 | .. | 19 | 3.2 | 1.5 | ... | 0.6 | 0 | 6 | 3 | 0 | .... | .. | Neurosyphilis; paresis |
| 12 | 2/12/26 | 40 | M | 0 | 0 | .. | .. | .... | .... | .... | 0.6 | 0 | 5 | 5 | 3 | .... | .. | Latent syphilis |
| 13 | 6/24/24 | 52 | M | 0 | 0 | 57 | 105 | 4.6 | 1.7 | 6.8 | 0.6 | 0 | 5 | 3 | 0 | 0.0 | .. | Neurosyphilis |
| | 6/30/24 | .. | .. | .. | .. | 54 | 69 | 3.9 | 1.8 | 6.4 | 0.9 | 0 | 4 | 3 | 0 | 0.0 | .. | |
| 14 | 10/21/24 | 68 | M | 0 | .. | 28 | 27 | 2.2 | 1.5 | 7.7 | 0.2 | 0 | 5 | 2 | 1 | 0.0 | .. | Acute syphilis |
| 15 | 9/20/24 | 48 | M | 0 | 0 | .. | 28 | 2.8 | 1.6 | 6.5 | 0.6 | 0 | 5 | 3 | 0 | 0.5 | .. | Neurosyphilis |
| 16 | 4/ 7/24 | 42 | M | 0 | 0 | 30 | 35 | .... | .... | .... | 1.3 | 0 | 4 | 2 | 0 | 0.3 | 0 | Latent syphilis |

PART 2

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm | Jaundice | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test; Dye in Serum, per Cent | | | Galactose Tolerance Test | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 15 Minutes | 30 Minutes | 60 Minutes | | |
| 17 | 11/21/27 | 51 | F | 2 | 0 | 16 | 0.3 | 0 | 5.2 | .. | 8 | 4 | 0 | Latent syphilis |
| 18 | 1/12/28 | 44 | F | 0 | 0 | 33 | 0.2 | 0 | 4.6 | .. | 8 | 2 | .. | Neurosyphilis |
| 19 | 9/ 1/28 | 53 | M | 0 | 0 | 27 | 0.3 | 0 | .... | .. | 6 | 2 | .. | Neurosyphilis |
| 20 | 7/24/28 | 40 | M | 0 | 0 | 21 | 1.2 | 0 | .... | .. | 6 | 0 | .. | Neurosyphilis |
| 21 | 5/15/28 | 37 | M | 0 | 0 | 26 | 1.1 | 0 | .... | .. | 4 | 1 | .. | Neurosyphilis; tabes |
| 22 | 1/21/28 | 36 | M | 3 | 0 | 24 | 0.2 | 0 | 4.8 | .. | 4 | 0 | .. | Neurosyphilis |
| 23 | 12/28/28 | 56 | M | 0 | 0 | .. | 0.7 | 0 | 4.3 | .. | 2 | 0 | .. | Neurosyphilis |
| 24 | 4/ 4/28 | 44 | F | 1 | 0 | 25 | 0.2 | 0 | .... | .. | 2 | 0 | .. | Neurosyphilis |
| 25 | 10/20/26 | 39 | M | 0 | 0 | 28 | 0.2 | 0 | .... | .. | 1 | 0 | .. | Neurosyphilis |
| 26 | 4/23/27 | 49 | M | 0 | 0 | .. | 0.6 | 0 | 4.0 | .. | 1 | 0 | .. | Neurosyphilis |
| 27 | 4/15/25 | 59 | F | 0 | 0 | 28 | 0.5 | 0 | .... | 5 | 0 | 0 | .. | Latent syphilis |
| 28 | 5/ 5/25 | 52 | M | 0 | 0 | 23 | 0.2 | 0 | .... | 0 | 0 | 0 | .. | Neurosyphilis |
| 29 | 4/20/27 | 42 | F | 0 | 0 | 24 | 0.9 | 0 | 4.3 | .. | 0 | 0 | .. | Latent syphilis |
| 30 | 1/11/28 | 35 | M | 0 | 0 | 16 | 0.2 | 0 | 4.8 | .. | 0 | 0 | .. | Neurosyphilis |

was a moderate degree of jaundice, and the serum bilirubin was 7.9 mg. in each 100 cc. The patient was given a course of mercury rubs. This was followed by rapid fading of the jaundice and coincident disappearance of the lesions of the skin. The serum bilirubin content dropped to normal by Jan. 12, 1928. Thereafter the patient remained well.

The laboratory tests showed a characteristic curve of recovery. The serum bilirubin, which was moderately increased, rapidly returned to normal. A direct van den Bergh reaction was present at first, and this persisted for a considerable period after the serum bilirubin had returned to the normal level. There was no increase in the bile acids. The bromsulphalein test showed marked retention of dye during the period of jaundice. This returned to normal more slowly than did the serum bilirubin. The final examination, eight months after the onset of the icterus, showed normal responses to all tests.

TABLE 2 (case 31).—*Progress in an Illustrative Case of Hepatitis of Acute Syphilis*

| Date | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test: Dye in Serum, per Cent | | |
|---|---|---|---|---|---|---|---|
| | | | | | 15 Minutes | 30 Minutes | 60 Minutes |
| 12/29/27 | 14 | 7.9 | + | 5.1 | .. | 64 | 64 |
| 1/ 3/27 | .. | 4.4 | + | ... | .. | .. | .. |
| 1/12/28 | 23 | 1.6 | + | 4.6 | .. | 36 | 26 |
| 1/23/28 | 16 | 0.8 | + | 4.8 | .. | 12 | 10 |
| 2/ 4/28 | .. | 0.2 | + | 4.4 | .. | 4 | 2 |
| 2/21/28 | 25 | 0.1 | + | ... | .. | 6 | 2 |
| 7/23/28 | 25 | 0.2 | 0 | ... | .. | 4 | 4 |

## DIFFUSE HEPATITIS OF LATE SYPHILIS

The hepatic complications associated with secondary syphilis present a fairly uniform clinical picture. The hepatitis of late syphilis is variable, but Wile [15] called attention to the point that the various clinical manifestations of late hepatic syphilis are due to different phases in the evolution of the morbid process. Our experience confirms this view. From a clinical point of view, late hepatic syphilis may be classified into two groups: hepatitis, the active process, which may be diffuse, gummatous or of mixed character, and cirrhosis, the end-result. All degrees and modifications or combinations may be present, the symptoms depending on the extent and degree of localization of the destruction of hepatic tissue.

The clinical syndrome of diffuse syphilitic hepatitis is identical with that of the nonsyphilitic forms of hepatitis which are caused by infec-

15. Wile, U. J.: Two Unusual Phases of Hepatic Syphilis, Arch. Dermat. & Syph. **1**:656 (June) 1920; The Treatment of the Syphilitic Liver and Heart: A Therapeutic Paradox, Am. J. M. Sc. **164**:415, 1922.

tious, chemical or toxic agents. Hence, it is essential that collateral evidences of syphilis be demonstrated before it is assumed that the hepatic disease is of syphilitic origin. Recently, both Stokes and McCrae discussed the symptoms of hepatic syphilis; but only in the gummatous type do the clinical data indicate the syphilitic nature of the condition. In certain instances, prolonged periods of observation and treatment are necessary to permit of etiologic deductions; in others, the postmortem examination alone furnishes a basis for a final conclusion.

The diffuse form of hepatitis makes a most favorable response to treatment with mercury and potassium iodide. The use of mercury by mouth in small doses, a form of treatment now used by syphilologists only when stimulative effects are desired, is an advantageous way in which to start antisyphilitic treatment in these patients. This may be augmented in a few weeks by inunction, or by the intramuscular injection of a soluble mercurial salt. This mild form of treatment permits of a slow and gradual replacement fibrosis in the liver; at the same time, it allows full opportunity for the establishment of collateral circulation of the blood. Under such circumstances the use of the arsphenamines is contraindicated, a point noted by others. The injudicious administration of arsenical preparations in this type of case may lead to the rapid production of portal cirrhosis and marked hepatic insufficiency. The characteristics of the whole group may be seen in table 3. The following case is an example of this type of diffuse hepatitis.

Case 38 (table 3).—The patient came to the clinic in June, 1923, because of a history of gallstone colic. At admission he was found to have a slightly enlarged liver, and roentgenograms of the gallbladder showed the presence of stones. At the same time, the Wassermann reaction of the blood was positive. He received a course of antisyphilitic treatment consisting of six intravenous injections of arsphenamine, a total of 2.8 Gm., and twenty-nine intramuscular injections of succinimide of mercury of 1/6 grain (0.0108 Gm.) each. At the end of this course of treatment the edge of the liver was still readily palpable and extended one fingerbreadth below the costal border.

The patient was operated on on August 9, because of severe gallstone colic which developed during the course of the antisyphilitic treatment. At the operation, gallstones were found, in addition to diffuse hepatitis which the surgeon reported as probably syphilitic in nature.

Following an uneventful convalescence the patient was sent home, but he returned again in November, 1923, for further treatment. Bile was found in the urine at this time. During November and December he received six intravenous injections of arsphenamine for a total of 2.1 Gm. and six intramuscular injections of 1 grain (0.065 Gm.) each of an insoluble mercurial salt. In March, 1924, he reported that marked jaundice had developed. The jaundice persisted until the time of his return in May. Six duodenal lavages gave a fair return of bile but only slight symptomatic relief. It was believed that syphilitic hepatitis was the cause of his difficulty, and he was given twenty intramuscular injections of succinimide of mercury of 1/6 grain (0.0108 Gm.) each in conjunction with potassium iodide. The icterus disappeared. Following an interval of six months he

TABLE 3.—*Diffuse Hepatitis of Late Syphilis*

PART 1

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice, Graded 0 to 4 | Duration of Jaundice, Mos. | Spleen Enlarged, Graded 0 to 4 | Blood Nitrogen Partition, Mg. for Each 100 Cc. | | | | | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Phenoltetrachlorphthalein Test | | | | Fructose Tolerance Test | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Non-protein Nitrogen | Urea | Uric Acid | Creatinine | Amino-Acid Nitrogen | | | Dye in Serum, % | | | Dye in Urine, Mg. | | |
| | | | | | | | | | | | | | | | 15 Min. | 1 Hr. | 2 Hr. | | | |
| 32 | 5/28/24 | 36 | M | 0 | 1 | 1 | 0 | 39 | 49 | ... | 1.7 | 6.8 | 9.4 | + | .. | .. | .. | ... | .. | |
| | 6/ 4/24 | .. | .. | .. | .. | .. | .. | .. | .. | ... | ... | ... | 2.4 | ± | 33 | 11 | 7 | 1.0 | .. | Improving |
| | 6/16/24 | .. | .. | 0 | 0 | .. | .. | 41 | 38 | 1.9 | 2.1 | 6.3 | 2.0 | 0 | 24 | 20 | 3 | 2.0 | .. | |
| | 6/24/24 | .. | .. | 0 | 0 | .. | .. | 37 | 39 | 2.2 | 1.9 | 5.8 | 0.6 | 0 | 8 | 2 | 0 | 0.6 | 0 | Jaundice cleared |
| 33 | 10/22/24 | 44 | M | + | 4 | .. | .. | 29 | 30 | 2.7 | 1.5 | 6.4 | 16.3 | + | 24 | 24 | 20 | 3.1 | .. | Neurosyphilis |
| | 11/ 5/24 | .. | .. | .. | 4 | .. | .. | 33 | 27 | 2.7 | 0.8 | 6.6 | 10.9 | + | 24 | 22 | 14 | 2.6 | .. | |
| | 11/20/24 | .. | .. | .. | 3 | .. | .. | .. | 17 | 2.6 | 1.1 | 6.1 | 6.4 | + | 20 | 20 | 18 | 3.0 | .. | |
| | 12/12/24 | .. | .. | .. | 2 | .. | .. | 29 | 29 | 3.1 | 1.3 | 5.9 | 5.4 | + | 22 | 25 | 22 | 2.5 | .. | Improving slowly |
| 34 | 1/24/25 | 38 | M | 3 | 1 | 15 | 0 | .. | 23 | 2.9 | 1.6 | ... | 3.7 | + | 20 | 21 | 17 | ... | .. | |
| | 2/18/25 | .. | .. | .. | .. | .. | .. | .. | 26 | 2.4 | 1.2 | ... | 0.9 | + | 6 | 2 | 0 | 0.5 | .. | Improving |
| 35 | 7/21/24 | 42 | M | 0 | 1 | .. | 0 | 24 | 34 | 2.8 | 1.2 | 5.9 | 3.2 | + | 16 | 22 | 13 | ... | .. | Latent syphilis; jaundice clearing |
| 36 | 1/13/25 | 54 | M | 2 | 1 | 1 | 0 | .. | 25 | ... | ... | ... | 1.0 | ± | 8 | 3 | 3 | ... | .. | Neurosyphilis; jaundice nearly gone |
| 37 | 8/ 5/24 | 49 | F | 10 | 0 | .. | 0 | 34 | 23 | 2.3 | 1.4 | 6.3 | 0.5 | 0 | 10 | 9 | 3 | 0.4 | .. | Latent syphilis; jaundice cleared |
| | 8/ 9/24 | .. | .. | 10 | 0 | .. | 0 | 30 | 23 | 2.3 | 1.2 | 4.8 | 0.6 | 0 | 13 | 9 | 2 | 0.4 | .. | Laparotomy for other cause; diagnosis confirmed |
| 38 | 5/ 6/24 | 46 | M | 8 | 2 | 15 | + | 25 | 32 | 3.8 | 1.9 | 6.1 | 9.7 | + | 23 | 36 | 26 | 2.5 | .. | Laparotomy for other cause; diagnosis confirmed |
| | 5/24/24 | .. | .. | .. | 2 | .. | .. | 24 | 26 | 3.2 | 1.0 | 5.9 | 9.4 | + | 22 | 25 | 24 | 1.9 | 0 | |
| | 6/10/24 | .. | .. | .. | 2 | .. | .. | 20 | 25 | 2.4 | 1.4 | 5.5 | 6.4 | + | 14 | 14 | 13 | 0.6 | 0 | Improving with treatment |
| | 11/24/24 | .. | .. | + | 1 | .. | 0 | .. | 53 | 4.2 | 1.9 | ... | 1.4 | + | 12 | 7 | 3 | 0.6 | .. | |
| | 6/20/25 | .. | .. | .. | .. | .. | .. | .. | 44 | ... | ... | ... | 1.7 | + | 9 | 7 | 0 | ... | .. | (continued in part 2) |

PART 2

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice, Graded 0 to 4 | Duration of Jaundice, Months | Spleen Enlarged, Graded 0 to 4 | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test; Dye in Serum, per Cent | | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | 15 Minutes | 30 Minutes | 1 Hour | |
| 38 | 1/24/27 | 49 | M | + | 0 | .. | 0 | 43 | 0.8 | 0 | 6.1 | .. | 10 | 2 | Syphilitic hepatitis, recovered |
| 39 | 5/20/26 | 32 | M | 1 | 3 | 2 | 1 | 20 | 21.4 | + | ... | .. | .. | .. | Syphilitic hepatitis |
| | 5/24/26 | .. | .. | .. | .. | .. | .. | 25 | 18.3 | + | 4.8 | 90 | 90 | 64 | |
| | 5/28/26 | .. | .. | .. | .. | .. | .. | 30 | 10.3 | + | ... | 100 | 64 | 64 | Improving |
| | 7/ 2/26 | .. | .. | .. | 0 | .. | .. | 25 | 1.2 | + | 3.4 | .. | 10 | 0 | Free of jaundice for 1 month |
| 40 | 2/27/28 | 46 | M | 5 | 2 | 10 | 1 | 41 | 7.2 | + | ... | .. | 68 | 68 | Syphilitic hepatitis |
| 41 | 8/23/27 | 46 | M | .. | 1 | .. | 0 | 29 | 5.2 | + | ... | .. | .. | .. | Syphilitic hepatitis |
| | 1/18/28 | .. | .. | .. | .. | .. | .. | 32 | 2.2 | + | 6.2 | .. | 36 | 34 | |
| | 2/ 9/28 | .. | .. | 1 | 1 | .. | 0 | 29 | 1.6 | + | 7.0 | .. | 30 | 30 | |
| | 3/ 1/28 | .. | .. | .. | .. | .. | .. | 23 | 1.1 | + | ... | .. | 30 | 30 | Improving with treatment |
| | 8/ 6/28 | .. | .. | .. | .. | .. | .. | 38 | 1.4 | + | ... | .. | 26 | 20 | |
| 42 | 1/ 4/27 | 51 | F | 0 | 0 | .. | 0 | 17 | 0.8 | 0 | ... | .. | 14 | 12 | Three years after recovery |
| 43 | 2/17/28 | 41 | M | .. | .. | .. | .. | .. | 0.2 | 0 | 4.5 | .. | 0 | 0 | Three years after recovery |

took forty mercurial inunctions. During July and September, while at home, the patient had two attacks of jaundice; each lasted about a month, and both subsided following a course of mercury intramuscularly. Since June, 1925, frequent examinations, in conjunction with the use of mercurial inunctions and potassium iodide, have maintained good health.

The functional tests are recorded in table 3.

When the patient was seen in May, 1924, the serum bilirubin content was elevated, 9.7 mg. in each 100 cc., and there was a direct van den Bergh reaction. The serum bilirubin decreased rapidly as the jaundice cleared. When the patient was seen in November, 1924, the serum bilirubin was normal and it has remained so. The direct van den Bergh reaction persisted for a considerable period after the serum bilirubin had returned to normal, but eventually it was replaced by the indirect reaction. The phenoltetrachlorphthalein test showed a marked retention of dye during the period of jaundice. This slowly decreased, and a normal reaction was found in June, 1925. A bromsulphalein test in January, 1927, likewise gave a negative reaction. A negative reaction was obtained in the fructose tolerance test during the period when the patient was still jaundiced.

This patient had syphilitic hepatitis in addition to the gallstones. He was treated with arsphenamine and mercury, following which jaundice and clinical signs of mild hepatitis developed. Under the continued use of mercury and potassium iodide he responded favorably, from both the clinical and the laboratory standpoint. Observation over a period of five years warrants a diagnosis of diffuse syphilitic hepatitis.

### GUMMATOUS HEPATITIS (HEPAR LOBATUM)

Gummatous involvement of the liver, especially when it takes the form of a typical hepar lobatum (table 4), offers the most readily diagnosed clinical picture of hepatic syphilis and the one most frequently suspected from clinical observations. Carcinoma, abscess, cystic disease, simple hypertrophy, cholelithiasis and splenomegaly at times offer difficult differential problems. In such cases, a final diagnosis must be made in part by exclusion and in part by the aid of the various laboratory tests available. When the patient has miliary gummas which do not enlarge the liver sufficiently to make it palpable, clinical differentiation is much more difficult than when a nodular or botryoid liver is present. Clinical differentiation of diffuse syphilitic hepatitis and miliary gummas may be impossible. Similarly, patients with gummatous livers, as a rule, have also varying degrees of diffuse scarring or cirrhosis. When ascites develops in such cases the differential diagnosis of gummatous hepatitis and portal cirrhosis may be exceedingly difficult. Treatment, as in diffuse syphilitic hepatitis, should be mild and the response to mercury and iodides is excellent. The following case demonstrates the value of such treatment. The arsphenamines alone are not indicated in the treatment for this form of hepatic syphilis. When other complications demand their use, it must be recognized that unusual circumstances are present, and corresponding care must be taken.

TABLE 4.—*Gummatous Hepatitis*

PART 1

| Case | Date | Age, Years | Sex | Liver Enlarged, Graded 0 to 4 | Liver Nodular | Spleen Enlarged | Blood Nitrogen Partition, Mg. for Each 100 Cc.: Non-protein Nitrogen | Blood Urea | Uric Acid | Creatinine | Amino-Acid Nitrogen | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Phenoltetrachlorphthalein Test: Dye in Serum, per Cent: 15 Minutes | 1 Hour | 2 Hours | Dye in Urine, Mg. | Fructose Tolerance Test | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 44 | 8/18/25 | 42 | F | 1 | + | 0 | .. | 23 | ... | ... | ... | 1.1 | ± | 17 | 17 | 10 | 0.5 | .. | Gumma found at operation in 1924; now healed |
| 45 | 6/18/25 | 66 | M | 2 | 0 | 0 | .. | 44 | ... | ... | ... | 1.6 | ± | 17 | 9 | .. | ... | .. | Ascites |
| 46 | 7/31/25 | 36 | M | 2 | + | 0 | .. | 27 | ... | ... | ... | 0.3 | 0 | 15 | 13 | 8 | ... | .. | |
| 47 | 1/28/25 | 43 | F | 3 | + | + | .. | 24 | ... | ... | ... | 1.2 | 0 | 15 | 5 | 5 | ... | .. | Gumma of liver |
| 48 | 2/25/25 | 41 | F | 0 | 0 | 0 | .. | 25 | 2.8 | 1.8 | ... | 0.5 | 0 | 12 | 3 | 0 | ... | .. | Gumma in 1917; now healed |
| 49 | 11/ 4/25 | 38 | M | 2 | 0 | 0 | .. | 24 | ... | ... | ... | 0.8 | 0 | 8 | 3 | 0 | ... | .. | |
| 50 | 8/ 4/24 | 51 | F | 2 | 0 | 0 | 31 | 27 | 1.8 | 1.4 | 5.8 | 0.8 | 0 | 7 | 3 | 0 | ... | 0 | Gumma found at operation in 1910; now healed |
| | 8/21/24 | .. | .. | .. | .. | .. | 38 | 13 | 2.6 | 1.4 | 4.4 | 1.4 | 0 | 8 | 3 | 0 | ... | 0 | |
| 51 | 3/24/25 | 36 | M | 3 | + | ++ | .. | 46 | 3.3 | 1.5 | ... | 0.7 | 0 | 7 | 6 | 3 | ... | .. | Gumma found at necropsy; ascites |
| 52 | 9/ 9/24 | 44 | M | 2 | + | 0 | 30 | 30 | 3.4 | 1.3 | 5.8 | 1.5 | 0 | 11 | 7 | 5 | ... | .. | |
| | 11/19/24 | .. | .. | 1 | + | 0 | 34 | 32 | 3.9 | 1.2 | 6.9 | 1.6 | 0 | 15 | 6 | 0 | ... | .. | Improving with treatment |
| | 12/ 2/24 | .. | .. | .. | .. | .. | 28 | 37 | 4.2 | 1.1 | 6.8 | 0.9 | 0 | 12 | 5 | 2 | 0.8 | .. | |
| | 4/ 1/25 | 45 | .. | .. | .. | .. | .. | 41 | ... | ... | ... | 0.6 | 0 | 12 | 7 | 2 | 0.9 | .. | (continued in part 2) |

PART 2

| Case | Date | Age, Years | Sex | Liver Enlarged, Graded 0 to 4 | Liver Nodular | Spleen Enlarged, Graded 0 to 4 | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. Blood | Bromsulphalein Test Dye in Serum, per Cent: 15 Minutes | 30 Minutes | 1 Hour | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 52 | 9/ 9/27 | 47 | M | 1 | + | 0 | 22 | 0.3 | 0 | ... | .. | 14 | 4 | Gumma in 1924; now healed |
| 53 | 7/ 9/25 | 36 | M | 2 | + | 0 | 15 | 0.4 | 0 | ... | 20 | 6 | 3 | Gumma of liver |
| | 4/ 1/26 | 37 | .. | .. | .. | .. | 25 | 0.5 | 0 | 3.9 | 36 | 8 | 2 | Later, after treatment |
| | 8/15/27 | 38 | .. | .. | .. | .. | 34 | 0.9 | 0 | ... | .. | 28 | 8 | |
| | 9/15/28 | 39 | .. | .. | .. | .. | 30 | 0.9 | 0 | ... | .. | 14 | 4 | |
| 54 | 6/22/26 | 45 | F | 2 | + | 0 | .. | 0.6 | 0 | ... | .. | 20 | 12 | Gumma of liver |
| | 7/31/26 | .. | .. | 1 | + | 0 | .. | 0.6 | 0 | 4.4 | .. | 10 | 0 | Later, after treatment |
| 55 | 12/16/26 | 44 | M | 2 | 0 | 0 | 36 | 0.2 | 0 | 4.2 | .. | 18 | 12 | Gumma found at operation |
| 56 | 7/10/25 | 43 | F | 3 | + | + | 24 | 0.2 | 0 | ... | 8 | 4 | 0 | Gumma of liver |
| | 6/16/26 | 44 | .. | .. | .. | .. | .. | 0.5 | 0 | 6.3 | .. | 20 | 3 | Later, after treatment |
| | 6/23/27 | 45 | .. | .. | .. | .. | 27 | 0.5 | 0 | ... | .. | 2 | 0 | |
| 57 | 12/21/27 | 39 | F | 0 | 0 | 0 | 32 | 0.2 | 0 | 5.1 | .. | 8 | 0 | Gumma in 1917; now healed |
| 58 | 10/20/26 | 47 | F | 4 | 0 | 0 | 13 | 0.3 | 0 | ... | .. | 4 | 0 | Gumma of liver |
| | 3/ 1/27 | .. | .. | 2 | .. | + | 17 | 0.5 | 0 | 3.6 | .. | 14 | 8 | Later, after treatment |
| | 11/ 3/27 | 48 | .. | 2 | .. | 1 | 31 | 1.0 | 0 | ... | .. | 2 | 0 | |
| | 9/19/28 | 49 | .. | 4 | .. | + | .. | 1.1 | 0 | ... | .. | 6 | 2 | |
| 59 | 6/16/26 | 40 | F | 0 | 0 | 0 | .. | 0.7 | 0 | ... | .. | 4 | 2 | Gumma found at operation in 1920; now healed |

CASE 52 (table 4).—The patient came to the clinic in September, 1924, complaining of soreness in the right upper quadrant of the abdomen and gave a history that during the last four years he had had frequent attacks of pain in the upper part of the right side of the abdomen, with soreness and tenderness on pressure in the region of the liver. Even a deep breath would cause discomfort. Gastro-intestinal upset or loss of appetite had not been noted, and there was not any history of chills, fever or jaundice. He had lost about 10 pounds (4.5 Kg.) in weight.

General examination showed the edge of the liver to be 5 cm. below the costal margin, with palpable irregular nodules on the border. The spleen apparently was not enlarged. The Wassermann reaction of the blood was strongly positive, and results of examination of the spinal fluid were negative. The patient did not receive arsphenamine at any time; the treatment consisted solely of mercurial inunctions and iodides. The subcostal mass rapidly disappeared under treatment, and the patient now weighs more than his previous maximal weight and is in good general condition.

This case demonstrates the value of treatment by mercurials and iodides in gummatous hepatitis. The arsphenamines are not indicated in the treatment for this form of hepatic syphilis unless other complications of syphilis demand their use, and then only under extreme circumstances.

In the gummatous form of disease of the liver there are numerous circumscribed areas of destruction of tissue of the liver, and hence more effort at compensation is possible than in diffuse hepatic involvement. The frequency with which livers with gummatous involvement may become greatly enlarged before producing few and insignificant constitutional symptoms may be cited as an example of the efforts at compensation which are made by the body. If judiciously treated, this group of patients invariably gives a highly favorable therapeutic response to the use of mercury and potassium iodide. During treatment the serum bilirubin (table 4) decreased slightly in this case, but it at no time exceeded the usual limits of normal. None of the patients with gumma was jaundiced, and the serum bilirubin was not increased. An indirect van den Bergh reaction was obtained in all patients. The fructose tolerance test was done in two instances, with negative results. The bile acids in the blood were not increased. The phenoltetrachlorphthalein test showed slight retention of dye in the case cited, and there was no change during the course of treatment, for in the majority of the cases of gumma which were studied there was a slight retention of dye, whereas normal dye readings were obtained in the remainder. The presence of enlarged nodular livers in the majority of these cases indicated the presence either of well developed gummas or of the scars resulting from the healing of such lesions. With localized lesions of this type the remainder of the liver may be relatively intact and free from functional

interference. Greene, McVicar, Rowntree and Walters [16] pointed out that in carcinomatous invasion of the liver the degree of abnormality in the various functional tests depends on the interference with activity of the liver as a whole. Unless there is infringement of or reduction in the normal reserve, a localized lesion such as a metastatic nodule cannot be demonstrated by functional tests. The same condition of affairs attends the demonstration of a gumma by these tests.

### CHRONIC HEPATITIS

The rôle played by syphilis in the development of hepatic cirrhosis has been a subject of great controversy. In the past, especially before the introduction of the Wassermann test, syphilis frequently was thought to be one of the chief etiologic agents in hepatic disease, and the use of mercury and iodides in cases of cirrhosis of the liver was recommended almost as a routine. We now recognize that there are many cases of cirrhosis in which there is no evidence, clinical, serologic or pathologic, of the presence of syphilis, and Greene, McVicar, Snell and Rowntree [17] recently reported a study of various tests for hepatic function in a series of cases of cirrhosis in which syphilis could be excluded as an etiologic agent. Nevertheless, cirrhosis is often met with in cases of syphilis, and the possibility of an etiologic relationship should not be dismissed. Both biliary and portal types of cirrhosis occur.

### CHRONIC HEPATITIS WITH JAUNDICE (BILIARY CIRRHOSIS)

In the discussion of the different forms of hepatic cirrhosis in nonsyphilitic cases the close relationship between cases of subacute hepatitis with jaundice and those of biliary cirrhosis without obstruction to the biliary passages was pointed out. The same relationship is to be observed in the syphilitic patient. We have distinguished the diffuse hepatitis of late syphilis from biliary cirrhosis of apparently syphilitic origin but recognize that the distinction probably is one of degree and stage of involvement and so is not clearly defined. Jaundice, frequently intermittent in type, malaise, loss of weight, diffuse enlargement of the liver and increase in the serum bilirubin with dye retention are characteristic features of both. Obviously when the condition has been so severe and of such duration as to permit of a diagnosis of cirrhosis, the prognosis is correspondingly more serious. Care is necessary in the institution of therapeutic measures. Treatment should be mild and

16. Greene, C. H.; McVicar, C. S.; Rowntree, L. A., and Walters, W.: Diseases of the Liver: IV. Functional Tests in Cases of Carcinoma of the Liver and Biliary Tract, Arch. Int. Med. **36**:542 (Oct.) 1925.

17. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: Diseases of the Liver: VI. A Comparative Study of Certain Tests for Hepatic Function in Cases of Cirrhosis of the Liver, Arch. Int. Med. **40**:159 (Aug.) 1927.

should be given cautiously to avoid too rapid fibrosis with consequent aggravation of the cirrhosis. The case reported is one of biliary cirrhosis in which it was possible to follow the whole course of development of this condition.

CASE 60 (table 5).—A married woman, aged 37, came to the clinic on Nov. 26, 1923, deeply jaundiced and complaining of intermittent attacks of icterus for the preceding seventeen months. She gave a history of varying degrees of pain in the right upper abdominal quadrant, associated with clay-colored stools, dark urine, generalized pruritus and nausea. She had had six attacks of from two to three weeks' duration. She lost 14 pounds (6.4 Kg.) in seventeen months.

On admission the patient was markedly jaundiced. The edge of the liver was felt 5 cm. below the costal border, and the spleen was just palpable. The Wassermann reaction of the blood was reported strongly positive, but examination of the cerebrospinal fluid gave negative results. Roentgenograms of the stomach and gallbladder were negative. Mild secondary anemia also was present. The

TABLE 5 (case 60).—*Progress in an Illustrative Case of Syphilitic Cirrhosis: Biliary Cirrhosis*

| Date | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Phenoltetrachlorphthalein Test: Dye in Serum, per Cent 15 Min. | 1 Hr. | 2 Hr. | Dye in Urine, Mg. | Bromsulphalein Test: Dye in Serum, per Cent 15 Min. | 30 Min. | 60 Min. | Fructose Tolerance Test |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11/26/23 | 10 | 13.1 | + | ... | 30 | 26 | 23 | 2.5 | .. | .. | .. | .. |
| 1/24/24 | 21 | 2.0 | 0 | ... | 4 | 3 | 2 | 0.0 | .. | .. | .. | .. |
| 4/16/24 | 13 | 4.8 | ± | ... | 23 | 25 | 20 | 2.2 | .. | .. | .. | 0 |
| 8/19/24 | 19 | 9.2 | + | ... | 24 | 26 | 26 | 3.2 | .. | .. | .. | .. |
| 9/27/24 | 23 | 4.2 | + | ... | 33 | 20 | 20 | 1.2 | .. | .. | .. | .. |
| 12/ 2/24 | 32 | 3.0 | + | ... | 15 | 13 | 8 | 1.2 | .. | .. | .. | .. |
| 5/ 7/25 | .. | 5.1 | + | ... | 22 | 25 | 22 | 1.9 | .. | .. | .. | .. |
| 6/ 6/25 | 11 | 8.2 | + | ... | 24 | 18 | 16 | ... | .. | .. | .. | .. |
| 9/15/25 | 10 | 5.6 | + | ... | 20 | 30 | 20 | 4.5 | .. | .. | .. | .. |
| 4/ 6/26 | 33 | 6.8 | + | 6.8 | .. | .. | .. | ... | 40 | 26 | 32 | .. |
| 10/ 4/27 | .. | 3.4 | + | 3.4 | .. | .. | .. | ... | .. | 36 | 32 | .. |
| 8/27/28 | .. | 5.1 | + | ... | .. | .. | .. | ... | .. | 40 | 36 | .. |

patient was given a month's preparation with mercurial inunctions and potassium iodide, and at the end of this time six injections of neoarsphenamine for a total of 2.9 Gm. were given. She left the hospital on Feb. 12, 1924, much improved and without signs of jaundice. The liver was slightly reduced in size, but the spleen was still palpable.

On April 14, 1924, the patient returned with moderate jaundice, although she had not had abdominal pain since the previous visit. The liver and spleen apparently were unchanged in size. A further course of mercury was instituted at home. She returned to the clinic on Aug. 18, 1924, weighing 118 pounds (53.5 Kg.); she had gained 12 pounds (5.4 Kg.). The edge of the liver was hard and readily palpable. There was moderate jaundice with a serum bilirubin content of 9.2 mg. in each 100 cc. Six intravenous injections of neoarsphenamine for a total of 2.6 Gm. were given in conjunction with succinimide of mercury. At the end of this course of treatment the serum bilirubin content was reported as 4.2 mg. The next period of observation was in December, 1924, at which time the patient looked and felt much better than on any previous visit. The jaundice was somewhat less, and the serum bilirubin content was 3.0 mg. The next observation period was in May, 1925, when she returned slightly jaundiced. Another course

of mercury by mouth and six small doses of neoarsphenamine, a total dosage of 1.6 Gm., made her feel better, although there was no particular change in the degree of icterus. The Wassermann reaction of the blood remained positive. In September, 1925, she was still jaundiced. Both the liver and the spleen seemed somewhat enlarged. At this time she was given intramuscular injections of potassium bismuth tartrate with butyn, 0.2 Gm., once a week. The icterus entirely disappeared following this treatment and did not reappear until April of the following year when it gradually returned, associated with a sense of biliousness. The serum bilirubin content at that time was reported as 6.8 mg. Several periods of observation since have shown the same degree of retention of the dye and variations of serum bilirubin. Three periods of jaundice with spontaneous remissions have occurred, not associated with abdominal pain or colic. Roentgenograms of the gallbladder remain negative.

The outstanding change in this six year period has been a definite increase in the size of the liver and the spleen, constant retention of dye and increase in the serum bilirubin. The diagnosis was diffuse syphilitic hepatitis slowly progressing to the stage of hypertrophic cirrhosis.

The functional studies in this case have paralleled the clinical status. The value of frequent and repeated tests is exemplified in table 5. When the patient first was seen the bilirubin was markedly elevated, and there was a direct van den Bergh reaction and moderate retention of phenoltetrachlorphthalein. Under treatment, there was initially a return to normal as in the cases of diffuse syphilitic hepatitis previously discussed. When the patient was seen in April, 1924, the retention of dye was proportionally much greater than the increase in jaundice. This disproportion between the two readings we believe is evidence of the permanent injury to the liver associated with the development of cirrhosis. Since then there has been no significant change in the tests. The bilirubin has remained elevated, with a direct van den Bergh reaction, and there has been marked retention of both phenoltetrachlorphthalein and bromsulphalein.

### CHRONIC HEPATITIS WITH ASCITES (PORTAL CIRRHOSIS)

Syphilis apparently was the chief etiologic agent in the cases of portal cirrhosis which we report in table 6, although in a few there was an additional history of chronic alcoholism. It is possible, too, that syphilis, although not of itself producing portal cirrhosis, may render the liver more susceptible to those noxious agents ordinarily responsible for the development of the latter condition. Finally, the effect of the modern intensive type of treatment for syphilis, particularly that with arsenical preparations, must not be overlooked as a cause of portal cirrhosis in such cases. This question will be discussed later in connection with the hepatic complications of treatment. Without more precise knowledge regarding the etiology of cirrhosis, it is manifestly impossible to make a more dogmatic statement. We are interested rather

TABLE 6.—*Syphilitic Cirrhosis: Portal Cirrhosis*

PART 1

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Ascites, Graded 0 to 4 | Duration of Ascites, Months | Spleen Enlarged, Graded 0 to 4 | Jaundice, Graded 0 to 4 | Blood Nitrogen Partition, Mg. for Each 100 Cc.: Non-protein Nitrogen | Urea | Uric Acid | Creatinine | Amino-Acid Nitrogen | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Phenoltetrachlorphthalein Test: Dye in Serum, per Cent: 15 Min. | 1 Hr. | 2 Hr. | Dye in Urine, Mg. | Fructose Tolerance Test | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 61 | 4/18/24 | 41 | M | 2 | 3 | 4 | 2 | 2 | 23 | 19 | 2.8 | 1.4 | 6.5 | 15.6 | + | 24 | 24 | 24 | 4.2 | .. | Jaundice; died 2 mo. later |
| 62 | 4/ 1/26 | 60 | M | 0 | 1 | 1 | 0 | 0 | .. | 16 | ... | ... | ... | 2.3 | ± | 20 | 20 | 10 | 3.5 | .. | Necropsy |
| 63 | 4/13/25 | 56 | M | + | 2 | 1 | + | 0 | 43 | 59 | 3.4 | 1.6 | ... | 2.8 | ± | 20 | 13 | 10 | 1.2 | .. | Died 3 months later |
| 64 | 6/15/25 | 33 | F | + | 0 | 0 | 0 | 0 | .. | 37 | ... | ... | ... | 3.2 | ± | 20 | 13 | 3 | 0.2 | .. | Ascites 7 years before |
| 65 | 11/ 7/24 | 40 | F | + | 4 | 18 | + | 0 | 33 | 29 | 3.2 | 1.4 | 6.1 | 1.3 | 0 | .. | 7 | 3 | ... | .. | On admission |
| | 12/10/24 | .. | .. | + | 0 | .. | + | 0 | 21 | 18 | 2.0 | 1.0 | 5.6 | 0.2 | 0 | 13 | 13 | 9 | ... | .. | Ascites-free after treatment |
| 66 | 5/22/24 | 62 | M | 0 | 3 | 1 | 0 | 0 | 90 | 150 | 4.7 | 1.9 | ... | ... | .. | 12 | 10 | 6 | ... | .. | Necropsy |
| 67 | 7/ 4/23 | 50 | M | ++ | 2 | 2 | 0 | 0 | .. | 32 | 3.1 | 1.6 | ... | ... | .. | 10 | 10 | 6 | 0.3 | .. | |
| 68 | 1/10/24 | 33 | F | + | 0 | 0 | 0 | 0 | 25 | 20 | ... | ... | ... | 0.8 | 0 | 12 | 8 | 3 | 1.3 | 0 | Ascites 2 years before; died of hemorrhage |
| 69 | 11/28/23 | 58 | M | 0 | 3 | 3 | 0 | 0 | .. | 39 | ... | ... | ... | 0.5 | 0 | 10 | 8 | 6 | 2.0 | .. | Died |
| 70 | 1/21/24 | 41 | M | 0 | 4 | 11 | 2 | 0 | 78 | 33 | ... | ... | ... | 0.7 | 0 | 10 | 4 | 1 | 0.4 | .. | |
| 71 | 11/13/24 | 43 | F | 0 | 3 | 1 | + | 0 | 94 | 114 | 6.0 | 9.0 | 5.9 | 0.6 | 0 | 10 | 4 | 0 | ... | .. | Nephritis; died |
| 72 | 9/ 8/23 | 47 | M | + | 2 | 48 | 0 | 0 | .. | 21 | ... | ... | ... | ... | .. | 7 | 4 | 0 | 0.0 | 0 | Improved with treatment |
| 73 | 3/12/25 | 41 | M | + | 3 | 5 | 1 | 0 | .. | 29 | 2.4 | 1.0 | ... | | | | | | | | |
| | | | | | | | | | | | | | | 1.3 | ± | 10 | 12 | 8 | 0.4 | .. | |
| | 5/10/25 | .. | .. | 3 | 1 | .. | + | 0 | .. | 13 | ... | ... | ... | 0.6 | ± | 8 | 13 | 8 | 0.9 | .. | Ascites clearing up with treatment (continued in part 2) |
| | 9/11/25 | .. | .. | 0 | 0 | .. | + | 0 | .. | 28 | ... | ... | ... | 2.5 | + | 20 | 18 | 13 | 3.5 | .. | |

PART 2

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Ascites, Graded 0 to 4 | Duration of Ascites, Months | Spleen Enlarged, Graded 0 to 4 | Jaundice, Graded 0 to 4 | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test: Dye in Serum, per Cent: 15 Min. | 30 Min. | 1 Hour | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 73 | 5/20/26 | 42 | M | 0 | 3 | 12 | + | 0 | 22 | 3.6 | + | 3.2 | 75 | 60 | 35 | |
| | 9/ 9/26 | .. | .. | + | 3 | .. | + | 1 | 42 | 6.8 | + | 3.7 | .. | .. | .. | Necropsy, weight of liver 1,120 Gm. |
| 74 | 1/12/28 | 45 | M | 0 | 2 | 4 | + | 0 | 20 | 3.3 | + | 4.7 | .. | 80 | 40 | Died of hemorrhage; necropsy |
| 75 | 4/ 1/26 | 60 | M | 0 | 1 | 1 | 0 | 0 | 19 | 3.8 | ± | ... | 95 | 75 | 50 | Necropsy |
| 76 | 12/ 7/26 | 50 | M | 0 | 3 | 1 | + | 2 | 25 | 3.8 | + | 4.0 | .. | 75 | 40 | |
| | 12/13/26 | .. | .. | .. | .. | .. | .. | .. | 28 | 2.6 | + | 4.0 | .. | 42 | 30 | |
| | 12/27/26 | .. | .. | .. | .. | .. | .. | .. | .. | 2.7 | + | 3.5 | .. | 40 | 30 | Died; necropsy |
| 77 | 5/ 3/27 | 64 | M | 9 | 4 | 12 | 5 | 0 | 26 | 1.2 | 0 | 5.3 | .. | 40 | 30 | |
| 78 | 10/ 3/25 | 41 | M | 0 | 3 | 36 | 0 | 0 | 37 | 2.2 | + | ... | .. | 44 | 20 | |
| 79 | 8/ 8/25 | 57 | M | 0 | 3 | 2 | 0 | 0 | 39 | 2.9 | + | ... | 52 | 40 | 26 | |
| 80 | 7/29/26 | 60 | M | 7 | 4 | 1 | + | 0 | 20 | 1.0 | 0 | 4.3 | .. | 24 | 14 | |
| 81 | 3/19/27 | 49 | M | 0 | 3 | 11 | 0 | 0 | 16 | 1.1 | ± | 3.6 | .. | 20 | 12 | |
| 82 | 11/10/26 | 50 | F | 4 | 2 | 3 | 3 | ± | 25 | 2.4 | 0 | 3.2 | .. | 18 | 14 | |
| | 11/19/26 | .. | .. | .. | .. | .. | .. | .. | 33 | 2.7 | 0 | 3.8 | .. | 32 | 16 | Improvement with treatment |
| | 11/22/26 | .. | .. | .. | .. | .. | .. | .. | 33 | 2.3 | 0 | 3.2 | .. | 22 | 12 | |
| | 11/30/26 | .. | .. | 4 | 2 | .. | 3 | 0 | 43 | 2.0 | 0 | 2.9 | .. | 28 | 16 | |
| | 12/ 7/26 | .. | .. | .. | 1 | .. | .. | .. | 20 | 1.1 | 0 | 4.5 | .. | 14 | 6 | |
| | 12/13/26 | .. | .. | .. | 0 | .. | .. | .. | 64 | 0.8 | 0 | 3.0 | .. | 14 | 2 | Ascites-free |
| | 12/24/26 | .. | .. | .. | 2 | .. | .. | .. | 32 | 1.2 | 0 | ... | .. | 32 | 22 | Recurrence of ascites |
| 83 | 2/ 3/27 | 63 | M | 0 | 2 | 3 | 0 | 0 | 32 | 1.0 | 0 | 5.0 | .. | 22 | 16 | |
| 84 | 11/18/26 | 33 | F | 3 | 4 | 5 | 0 | 0 | 27 | 0.0 | 0 | 3.6 | .. | 18 | 18 | |
| 85 | 12/18/25 | 50 | M | 5 | 0 | 0 | 0 | 0 | 18 | 0.7 | 0 | 2.8 | 36 | 20 | 4 | |
| | 9/17/27 | .. | .. | .. | .. | .. | .. | .. | 19 | 0.5 | 0 | 4.1 | .. | 14 | 6 | |

in a study of the changes shown by the different functional tests, and in the comparison between the changes found in the ordinary type of portal cirrhosis and the present group in which syphilis also is present.

The degree of cirrhosis present at the time the disease is recognized clinically may be roughly estimated by the size of the liver, particularly if it is small; by the degree of ascites, it being borne in mind that ascites occasionally will occur early in the course of the cirrhosis; by the presence of pain in the right upper abdominal quadrant; by splenomegaly, and by jaundice. The presence of hematemesis, or blood in the stools, is a complication to be dreaded; it suggests the presence of varices in the esophagus. In several of the cases in which therapeutic results were highly satisfactory the patients died suddenly from ruptured esophageal varicosities. The enlarged liver, and a slightly enlarged spleen, suggest early cirrhotic involvement in contrast to the small liver and large spleen which suggest extensive and long standing involvement. The treatment of a patient with such cirrhosis consists of the mild or tonic treatment for syphilis, aided by a diet with a low content of protein and a high content of carbohydrate, and by paracentesis when necessary. Antisyphilitic medication is a secondary consideration. The use of diuretics, as suggested by Rowntree, Keith and Barrier,[18] has given symptomatic relief in advanced cases. The following history is an example of such a case of portal cirrhosis of apparently syphilitic origin.

Case 73 (table 6).—A man, aged 38, with a history of alcoholism, came under our care in 1920 for treatment for early tabes dorsalis. He received, over a period of two and a half years, four courses of antisyphilitic treatment consisting of twenty-four intravenous injections of arsphenamine for a total dosage of 9.7 Gm., 200 mercurial inunctions, thirty-six intramuscular injections of succinimide of mercury, ⅙ grain (0.0108 Gm.), with potassium iodide during each course of mercury. The clinical and serologic result was highly satisfactory. Enlargement of the abdomen and edema of the ankles were noted in 1925 while the patient was confined to a hospital elsewhere by a fractured fibula and tibia. Because of the history of syphilis, with previous treatment, he was given seven intravenous injections of arsphenamine together with intramuscular injections of mercuric salicylate while he was convalescing from the fracture. Just before dismissal from the hospital, abdominal paracentesis had been done; following this, he returned to work and did not have any abdominal discomfort for six months.

The patient returned to the clinic in September, 1925, because of recurrence of the ascites. At that time the edge of the liver was 5 cm. below the costal border in the nipple line, and there was a divergence of opinion as to whether the spleen was palpable or not. He was placed on a salt-free diet, with a fluid intake limited to 600 cc. in twenty-four hours, and diuresis was induced with merbaphen. He improved considerably. He did not adhere to instructions after dismissal from the hospital, and again began drinking on the average of a quart of whisky a day. The ascites promptly recurred, and he returned in August, 1926, with

18. Rowntree, L. G.; Keith, N. M., and Barrier, C. W.: Novasurol in the Treatment of Ascites in Hepatic Disease, J. A. M. A. **85**:1187 (Oct. 17) 1925.

marked ascites, the edge of the liver just palpable at the costal border and the spleen markedly enlarged. While under observation he bled to death from a ruptured esophageal varix.

Necropsy revealed a small liver (1,120 Gm.) and an enlarged spleen (423 Gm.). The liver presented typical Laennec's cirrhosis; there were many nodules of hepatic tissue with depressed areas of fibrous tissue between the nodules. The pathologic appearance was that of typical portal cirrhosis and without any features to indicate the specific etiologic agent responsible for its development. The ruptured esophageal varicosity was readily demonstrated in addition to other pathologic processes which had no bearing on this discussion.

The difficulty in determining the etiologic factor from the clinical syndrome is emphasized by this case report; also, the fact mentioned elsewhere that cirrhosis of the liver is the end-result of injury to the liver from various causes.

The laboratory determinations in this group of patients did not differ from those found in the series of cases of nonsyphilitic cirrhosis reported by Greene, McVicar, Snell and Rowntree.[17] The serum bilirubin was normal or slightly increased over the level found in that series in the majority of the cases of syphilitic portal cirrhosis. In the case cited, it was normal when the patient was first seen. As his condition advanced, there was an increase in the serum bilirubin to a value slightly over the normal. One patient with frank jaundice had correspondingly elevated serum bilirubin. A direct van den Bergh reaction was obtained in those cases in which the serum bilirubin was elevated and in some with a normal amount of pigment.

Retention of dye was observed in the cases of cirrhosis. A normal response was noted in only one instance. This was true of both the phenoltetrachlorphthalein and the bromsulphalein tests, although the latter possibly showed slightly greater changes. With the development of jaundice, there was an increase in the degree of retention of dye. Treatment in this group and in the presence or absence of ascites apparently was without effect on the excretion of dye. The tolerance to fructose was normal in the two cases studied. There was no increase in the bile acids in the blood. The laboratory studies serve further to emphasize the permanent and irremediable nature of the injury to the liver in these cases of cirrhosis.

### THE HEPATIC COMPLICATIONS OF TREATMENT FOR SYPHILIS; POSTARSPHENAMINE JAUNDICE

The complications that develop in the liver during or shortly after a course of antisyphilitic treatment are disturbing and may be serious. There has been considerable discussion as to whether these reactions, particularly the jaundice, were the result of the toxic effects of arsphenamine, of mercury and iodides or of a secondary infectious agent. Possibly, too, a liver injured by syphilis or arsphenamine may

be unduly susceptible to the effect of the minor infections of everyday life. Without attempting to assume a strongly partisan attitude, we have been impressed with the fact that any of these factors may be at fault and that, in addition to the syphilis, some irrelevant entity, such as cholelithiasis, or carcinoma in the biliary system or adjacent viscera, may be the cause of jaundice in a patient recently treated for syphilis. O'Leary [19] emphasized the fact that the appearance of jaundice in a patient in whom a series of injections of arsphenamine or mercury has recently been completed, presents a problem of differential diagnosis which at times may require a long period of observation before definite conclusions are possible. Inadequate knowledge of the syndrome of early hepatic disease in general, with the inadequacy of the laboratory methods available at this time, and the fact that various factors will produce the same clinical syndrome, are the reasons for the present confusion in regard to this complication of jaundice. As is readily realized, the severity of the symptoms of this complication, for convenience called "postarsphenamine jaundice," is dependent on the degree of injury to the liver whether from arsenic, mercury, staphylococci, streptococci or syphilis. Table 7 with the accompanying case histories is presented to call attention to the various types of hepatic complications observed following treatment for syphilis and to the diagnostic and prognostic value of the tests of hepatic function in this complication.

Case 115 (table 7).—The patient came to the clinic in November, 1923, with asymptomatic neurosyphilis. The Kolmer modification of the Wassermann reaction of the blood was reported as strongly positive, graded 44. The Wassermann reaction of the spinal fluid was strongly positive, graded 44, the globulin test (Nonne) was positive, and the fluid contained 7 lymphocytes in each cubic millimeter. The colloidal benzoin reaction was 002 000 033 200 000. Results of a general examination were negative. The patient gave a history of having had an acute syphilitic infection in 1921. Previous to coming to the clinic he had received sixteen intravenous injections of neoarsphenamine, and twenty intramuscular injections of mercury salicylate. He had been taking mercury pills at irregular intervals for the last sixteen months.

Under our direction treatment was started on Nov. 16, 1923, the patient receiving seven intravenous injections of arsphenamine at weekly intervals, for a total dosage of 2.7 Gm. In addition, three intraspinal treatments were given according to the Swift-Ellis-Ogilvie modification, five intramuscular injections of 1 grain (0.065 Gm.) of mercury bichloride (bichloridol) at weekly intervals and ten intravenous injections of 100 cc. of a 10 per cent solution of sodium iodide. The patient was dismissed from the clinic on Jan. 2, 1924, and was advised to start on a course of forty mercurial inunctions of 50 grains (3.25 Gm.) each. He failed to take the rubs, but reported, February 4, that he was feeling well. About February 15, he complained of nausea, loss of ambition and appetite, malaise and pain in the bones and the muscles. These symptoms persisted until March 15, when jaundice

19. O'Leary, P. A.: Postarsphenamin Jaundice, M. Clin. North America **8**:1203, 1925.

appeared. The local physician who was called at this time advised an operation for the removal of gallstones. The operation was postponed for six weeks, during which time the jaundice became more intense, and the patient complained more of nausea, loss of weight and the constitutional symptoms so common in cases of infectious jaundice. Against our advice, the patient was operated on elsewhere for cholelithiasis; the diagnosis was based on the persistent painless jaundice. Gallstones were not found; the liver was reported to be somewhat enlarged and congested. Convalescence was somewhat protracted, and the patient remained in the hospital eight weeks, during which time the jaundice did not show a tendency to diminish.

The patient returned to the clinic, June 15, still slightly jaundiced. There was a small amount of free fluid in the abdomen, and slight edema of the ankles; the stools were still clay-colored, and the urine gave a positive reaction for bile. The wound had healed, leaving a small ventral hernia. The reaction of the blood by the Kolmer test still was reported as strongly positive. The serum bilirubin value was 3 mg. in each 100 cc. In view of the prolonged and protracted course of the jaundice, the patient was given daily intramuscular injections of succinimide of mercury and a 10 per cent solution of sodium iodide intravenously. Within a few days, he reported that he was feeling better, and he continued to improve rapidly.

This case is an example of a mild type of postarsphenamine jaundice which cleared up without leaving discernible injury in the liver. It is our impression that the jaundice was the result of the treatment that was instituted for syphilis; probably the arsphenamine was the cause.

The jaundice was subsiding when the patient was first observed, and the serum bilirubin content soon dropped to normal from the original value of 3 mg. A direct van den Bergh reaction was present at first, but later it became indirect. There was a lag in the response, however, and the direct van den Bergh reaction persisted for a month or more after the serum bilirubin content had dropped to within the usual limits of normal. There was moderate retention of phenoltetrachlorphthalein which persisted for a considerable period after all other evidence of injury to the liver had disappeared. It gradually decreased, and when the patient was last noted in March, 1927, there was a normal response to all tests.

Case 116 (table 7).—A man, aged 44, came to the clinic in February, 1926. He had a primary lesion followed by a secondary rash about twenty years before. When he was first examined there was no clinical evidence of activity, but the Wassermann reaction of the blood was strongly positive, graded 44, and the spinal fluid gave a positive globulin reaction and a colloidal gold curve indicative of syphilis. He was given a vigorous course of antisyphilitic treatment, and during a period of eighteen months he received eighteen injections of arsphenamine for a total of 8.3 Gm. and forty-two intramuscular injections of succinimide of mercury in 1/6 grain (0.0108 Gm.) doses. The last injection of arsphenamine was in February, 1927. The patient was well for a period but returned May 9, because of painless jaundice of four days' duration. He was in good condition apart from the jaundice. The liver and spleen were not palpable. The serum bilirubin content was 18.7 mg. in each 100 cc. He was given daily intravenous injections of

TABLE 7.—*Postarsphenamine Jaundice*

PART 1

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice, Graded 0 to 4 | Duration of Jaundice, Weeks | Spleen Enlarged, Graded 0 to 4 | Blood Nitrogen Partition, Mg. for Each 100 Cc. | | | | | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Phenoltetrachlorphthalein Test | | | | Fructose Tolerance Test | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Non-protein Nitrogen | Urea | Uric Acid | Creatinine | Amino-Acid Nitrogen | | | Dye in Serum, per Cent | | | Dye in Urine, Mg. | | |
| | | | | | | | | | | | | | | | 15 Min. | 1 Hr. | 2 Hr. | | | |
| 86 | 7/ 7/24 | 46 | M | + | 3 | 4 | 0 | 33 | 51 | 2.7 | 2.8 | 5.7 | 17.6 | + | 46 | 40 | 31 | 3.0 | . | Neurosyphilis; jaundice |
| | 7/10/24 | .. | .. | .. | 3 | .. | .. | 45 | 55 | 3.0 | 2.5 | 6.1 | 9.9 | + | 24 | 34 | 26 | 1.5 | .. | Improving with treatment |
| | 7/15/24 | .. | .. | .. | 2 | .. | .. | 47 | .. | 3.0 | 1.7 | 6.3 | 7.6 | + | 20 | 18 | 10 | 0.0 | .. | |
| | 7/28/24 | .. | .. | .. | 1 | .. | .. | 47 | 56 | 4.4 | 2.1 | 5.8 | 4.3 | + | 13 | 10 | 8 | 0.2 | .. | Dismissed from hospital |
| | 8/25/24 | .. | .. | .. | 0 | .. | .. | .. | .. | ... | ... | ... | 0.8 | ± | .. | .. | .. | ... | .. | One month later recovered |
| 87 | 9/17/24 | 56 | M | 0 | 3 | 3 | .. | .. | 24 | 1.9 | 1.8 | ... | 32.5 | + | 35 | 30 | 24 | 2.8 | .. | Neurosyphilis; jaundice |
| | 10/ 1/24 | .. | .. | .. | 3 | .. | .. | 39 | 30 | 2.1 | 1.3 | 6.8 | 4.8 | + | 13 | 13 | 9 | 2.4 | .. | Improving with treatment |
| | 10/ 6/24 | .. | .. | .. | 2 | .. | .. | 28 | 31 | 3.0 | 1.6 | 6.0 | 5.0 | + | 15 | 9 | 5 | 1.2 | .. | |
| | 10/13/24 | .. | .. | .. | 1 | .. | .. | .. | 28 | .. | 1.6 | .. | 4.4 | + | 8 | 5 | 3 | ... | .. | |
| | 11/12/24 | .. | .. | 4 | 1 | .. | .. | 41 | 25 | 2.2 | 1.5 | 6.9 | 3.8 | + | .. | 4 | 1 | 0.5 | .. | Jaundice nearly gone |
| 88 | 9/24/24 | 44 | M | 3 | 4 | 3 | 0 | 27 | 18 | 2.4 | 1.4 | 6.4 | 15.9 | + | 40 | 35 | 25 | 2.4 | .. | Neurosyphilis; jaundice |
| | 10/ 6/24 | .. | .. | .. | 3 | .. | .. | 31 | 23 | 3.6 | 1.7 | 6.4 | 3.1 | + | 13 | 13 | 10 | 0.7 | .. | Improving with treatment |
| | 10/14/24 | .. | .. | .. | 2 | .. | .. | 25 | 20 | 2.7 | 1.5 | 5.0 | 2.7 | + | 15 | 14 | 9 | 0.7 | .. | |
| | 12/ 5/24 | .. | .. | .. | 1 | .. | .. | 31 | 16 | 3.0 | 1.4 | 4.5 | 1.0 | 0 | 9 | 6 | 2 | 0.2 | .. | Recovered |
| | 2/26/25 | .. | .. | .. | 0 | .. | .. | .. | 24 | 2.7 | 1.1 | ... | 0.3 | 0 | 8 | 5 | 2 | ... | .. | Three months later |
| 89 | 9/22/24 | 60 | M | .. | 2 | 1 | .. | 31 | 27 | 2.9 | 1.7 | 7.9 | 5.6 | + | 11 | 20 | 20 | 1.4 | .. | Neurosyphilis; jaundice developing |
| | 9/30/24 | .. | .. | .. | 3 | .. | .. | 25 | 15 | 3.1 | 1.6 | 6.4 | 11.1 | + | 34 | 26 | 25 | ... | .. | |
| | 10/ 7/24 | .. | .. | ++ | 3 | .. | .. | 42 | 48 | 3.3 | 2.2 | 7.5 | 18.6 | + | 24 | 44 | 42 | ... | .. | Increasing jaundice |
| | 10/14/24 | .. | .. | .. | 4 | .. | .. | 26 | 15 | 2.4 | 1.7 | 6.8 | 18.8 | + | 27 | 30 | 30 | ... | .. | |
| | 10/17/24 | .. | .. | .. | 4 | .. | .. | 33 | 31 | 1.9 | 1.4 | 6.3 | 20.0 | + | 22 | 36 | 34 | 2.2 | . | Maximal jaundice |
| | 11/25/24 | .. | .. | .. | 0 | .. | .. | .. | 26 | 2.2 | 1.5 | ... | 1.7 | + | 6 | 3 | 1 | 0.0 | .. | Neurosyphilis; recovered 1 mo. later |
| 90 | 7/22/25 | 27 | F | 0 | 3 | 2 | 0 | .. | .. | ... | ... | ... | 14.8 | + | 24 | 36 | 34 | ... | .. | Neurosyphilis; jaundice |
| 91 | 9/15/24 | 46 | M | .. | 4 | .. | .. | 32 | 26 | 3.1 | 1.8 | 6.5 | 13.4 | + | 40 | 35 | 27 | ... | .. | Neurosyphilis; jaundice |
| | 9/23/24 | .. | .. | .. | 2 | .. | .. | 38 | 38 | 3.6 | 1.7 | 6.7 | 4.9 | + | 22 | 25 | 20 | 0.4 | .. | Improving with treatment |
| | 9/30/24 | .. | .. | .. | 0 | .. | .. | 26 | 18 | 3.0 | 1.7 | 5.7 | 1.8 | ± | 7 | 6 | 3 | 0.4 | .. | |
| | 11/10/24 | .. | .. | .. | 0 | .. | .. | 31 | 32 | 1.7 | 1.5 | 5.2 | 0.3 | 0 | 5 | 3 | 1 | 0.0 | .. | Complete recovery |
| 92 | 1/ 3/24 | 62 | M | 1 | 4 | 2 | 0 | 33 | 20 | ... | ... | ... | 8.2 | + | 30 | 28 | 15 | 2.0 | + | Latent syphilis; jaundice; recovering |
| 93 | 1/24/24 | 45 | M | 2 | 4 | 4 | 0 | 26 | 10 | ... | ... | ... | 10.0 | + | 30 | 20 | 17 | 3.5 | .. | Latent syphilis; jaundice; recovering |
| 94 | 4/ 3/25 | 38 | M | + | 1 | 2 | 0 | .. | 25 | ... | ... | ... | 6.7 | + | 26 | 24 | 20 | 2.0 | .. | Latent syphilis; jaundice |
| | 4/20/25 | .. | .. | 4 | 1 | .. | .. | .. | .. | ... | ... | ... | 4.2 | + | 13 | 22 | 18 | 0.6 | .. | Improving with treatment |
| | 4/25/25 | .. | .. | .. | 0 | .. | .. | .. | 18 | ... | ... | ... | 4.8 | + | 17 | 20 | 17 | ... | .. | |
| 95 | 6/21/23 | 32 | M | 0 | 3 | 1 | 2 | 40 | 60 | ... | 2.3 | 6.0 | ... | .. | 17 | 19 | 17 | 6.0 | .. | Latent syphilis; jaundice |
| | 6/30/23 | .. | .. | 0 | 3 | .. | .. | 26 | 26 | ... | ... | ... | ... | .. | 18 | 18 | 20 | 6.1 | .. | Slight improvement |
| | 7/ 9/23 | .. | .. | .. | 2 | .. | .. | 25 | 20 | ... | 1.3 | ... | ... | .. | 20 | 18 | 15 | 4.5 | .. | |
| | 7/23/23 | .. | .. | .. | 1 | .. | .. | 27 | 27 | ... | ... | ... | ... | .. | 15 | 11 | 3 | 2.0 | .. | Improving |
| | 8/ 3/23 | .. | .. | .. | 1 | .. | .. | 28 | 28 | ... | ... | ... | ... | .. | 11 | 7 | 3 | 0.8 | .. | Dismissed from hospital |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 96 | 8/ 6/24 | 36 | M | .. | .. | .. | .. | 27 | 14 | 1.9 | 1.1 | 5.6 | 7.6 | + | 18 | 22 | 22 | 1.9 | .. | Neurosyphilis; jaundice clearing |
| | 9/12/24 | .. | .. | .. | .. | .. | .. | 23 | 13 | ... | ... | ... | 0.7 | 0 | 6 | 3 | 0 | 0.0 | .. | Recovered |
| | 11/26/24 | .. | .. | .. | .. | .. | .. | .. | 15 | 2.3 | 1.3 | ... | 0.8 | 0 | 6 | 3 | 0 | 0.0 | .. | Three months later well |
| 97 | 1/15/26 | 52 | M | 3 | 1 | 12 | 0 | .. | .. | ... | ... | ... | 2.0 | + | 25 | 12 | 5 | 0.0 | .. | Neurosyphilis; recovering |
| 98 | 5/22/23 | 52 | M | 5 | 1 | 8 | 0 | .. | 21 | 2.7 | 1.4 | 5.4 | ... | .. | 15 | 15 | .. | ... | .. | Neurosyphilis; jaundice; recovering |
| | 7/ 8/24 | 53 | .. | .. | .. | .. | .. | 44 | 48 | 2.3 | 2.3 | 7.5 | 4.2 | 0 | 18 | 14 | 7 | 0.3 | .. | One year later residual cirrhosis |
| | 7/18/24 | .. | .. | .. | .. | .. | .. | 35 | .. | 2.8 | 2.8 | 6.9 | 2.5 | 0 | 17 | 16 | 6 | ... | .. | |
| | 5/ 7/25 | 54 | .. | .. | .. | .. | .. | .. | 44 | ... | ... | ... | 0.9 | 0 | 6 | 5 | 1 | ... | .. | |
| 99 | 3/ 3/24 | 33 | M | .. | 3 | 20 | 0 | 30 | 33 | ... | ... | ... | 5.4 | + | 14 | 14 | 14 | 3.0 | .. | Latent syphilis; jaundice; recovering |
| 100 | 8/ 4/24 | 36 | M | 0 | 1 | 2 | 0 | .. | 51 | 2.9 | 1.3 | ... | 3.2 | + | 9 | 10 | 5 | 0.5 | .. | Latent syphilis; jaundice |
| | 8/11/24 | .. | .. | .. | 0 | .. | .. | 31 | 12 | 2.5 | 1.5 | 6.1 | 1.6 | ± | 9 | 7 | 3 | 0.6 | .. | Recovering |
| 101 | 7/23/24 | 45 | M | .. | 1 | .. | 0 | 35 | 19 | 3.1 | 1.5 | 7.2 | 0.9 | + | 30 | 7 | 1 | ... | .. | Neurosyphilis |
| | 8/ 6/24 | .. | .. | .. | 1 | .. | .. | 34 | 19 | 1.7 | 1.2 | 5.8 | 1.8 | + | 11 | 12 | 8 | 0.6 | .. | Slight persistent jaundice |
| | 12/26/24 | .. | .. | .. | 1 | .. | .. | 37 | 19 | 3.1 | 1.1 | ... | 2.2 | 0 | 8 | 6 | 2 | 0.8 | .. | |
| 102 | 6/ 9/24 | 32 | M | 0 | 1 | 1 | 0 | 31 | 37 | 2.4 | 1.4 | 5.5 | 4.4 | + | 12 | 12 | 7 | ... | .. | Neurosyphilis; jaundice clearing |
| 103 | 8/26/24 | 58 | M | 0 | 1 | 4 | 0 | 23 | 23 | 3.1 | 1.5 | 5.6 | 3.4 | + | 17 | 10 | 5 | ... | .. | Latent syphilis; jaundice clearing |
| 104 | 6/23/24 | 53 | M | 1 | 0 | .. | 0 | 33 | 38 | 1.8 | 1.7 | 6.7 | 3.1 | + | 13 | 10 | 10 | 0.2 | .. | Neurosyphilis; jaundice 2 months before; recovered |
| 105 | 11/28/24 | 53 | M | 0 | .. | .. | .. | 18 | 12 | 3.8 | 0.9 | 6.0 | 0.6 | 0 | 11 | 4 | 2 | ... | .. | Neurosyphilis; jaundice clearing; 2 |
| | 1/20/25 | .. | .. | .. | .. | .. | .. | .. | 36 | 3.6 | 1.7 | 6.5 | ... | .. | 8 | 2 | 0 | 0.7 | .. | months later recovered |
| 106 | 11/20/24 | 50 | M | 0 | 1 | 4 | 0 | 41 | 36 | 3.5 | 1.8 | 7.5 | 3.7 | + | 14 | 8 | 4 | 1.0 | .. | Neurosyphilis; jaundice clearing |
| 107 | 9/ 2/24 | 30 | M | 0 | 0 | . | 0 | 31 | 25 | 2.7 | 1.4 | 6.7 | 0.8 | 0 | 9 | 6 | 0 | ... | .. | Neurosyphilis; jaundice 2 years before; recovered |
| 108 | 2/ 2/26 | 26 | M | 0 | 0 | .. | 0 | .. | 18 | ... | ... | ... | 0.8 | ± | 8 | 5 | 0 | ... | .. | Latent syphilis; jaundice 3 months before; recovered |
| 109 | 5/ 9/23 | 51 | M | 0 | 1 | 4 | 0 | .. | 26 | ... | ... | 4.7 | ... | .. | 11 | 7 | .. | ... | .. | Neurosyphilis; jaundice; recovering |
| 110 | 1/ 4/24 | 24 | M | + | 1 | 4 | .. | .. | 12 | ... | ... | ... | ... | .. | 10 | 8 | 7 | ... | 0 | Jaundice improving |
| | 7/21/24 | .. | .. | .. | .. | .. | .. | 29 | 31 | 2.2 | 1.4 | 6.0 | 0.3 | 0 | 7 | 3 | 0 | 0.8 | .. | Recovered |
| | 8/ 5/24 | .. | .. | .. | . | .. | .. | 27 | 26 | 2.3 | 1.4 | 5.8 | 0.9 | 0 | 8 | 3 | 0 | 0.5 | .. | Recovered |
| 111 | 2/ 2/24 | 26 | M | + | 0 | .. | .. | 31 | 23 | ... | ... | ... | 0.5 | 0 | 8 | 4 | 1 | ... | 0 | Latent syphilis; jaundice 2 years before; recovered |
| 112 | 12/19/24 | 39 | M | 0 | 0 | .. | 0 | 36 | 20 | 4.1 | 2.5 | 7.5 | 0.1 | 0 | 6 | 2 | 0 | 0.5 | .. | Latent syphilis; jaundice 6 months before; recovered |
| 113 | 6/10/25 | 45 | M | 0 | 0 | 0 | 0 | .. | 29 | ... | ... | ... | 0.9 | 0 | 7 | 3 | 0 | ... | .. | Neurosyphilis; jaundice 3 months before; recovered |
| 114 | 2/ 9/24 | 48 | M | + | .. | 0 | .. | 35 | 30 | 3.2 | 1.4 | ... | 1.0 | .. | 3 | 1 | 0 | 0.6 | .. | Neurosyphilis; jaundice 2 years before; recovered |
| 115 | 6/18/24 | 23 | M | .. | 1 | 8 | .. | 24 | 23 | 2.7 | 1.4 | 5.3 | 3.0 | + | .. | 7 | 4 | 0.6 | .. | Neurosyphilis; jaundice |
| | 6/30/24 | .. | .. | .. | 1 | .. | .. | 28 | 32 | 2.8 | 1.6 | 6.1 | 1.8 | + | 13 | 8 | 5 | 0.4 | .. | Gradual improvement with treatment |
| | 7/29/24 | .. | .. | .. | 0 | .. | .. | 24 | 28 | 2.1 | 1.5 | 5.5 | 1.4 | + | 13 | 28 | 4 | 0.5 | .. | |
| | 10/20/24 | .. | .. | .. | 0 | .. | .. | 25 | 16 | 2.9 | ... | 7.2 | 0.5 | 0 | 7 | 4 | 2 | 0.4 | .. | |
| | 11/13/24 | .. | .. | .. | 0 | .. | .. | 29 | .. | 5.6 | 1.3 | 6.8 | 0.5 | 0 | 10 | 6 | 1 | 0.0 | .. | (continued in part 2) |

TABLE 7.—*Postarsphenamine Jaundice—Continued*

PART 2

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice, Graded 0 to 4 | Duration of Jaundice, Weeks | Spleen Enlarged | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test: Dye in Serum, per Cent | | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | 15 Min. | 30 Min. | 60 Min. | |
| 115 | 3/17/27 | 26 | M | .. | 0 | .. | 0 | 18 | 0.2 | 0 | 4.6 | .. | 2 | 0 | Jaundice 3 years before; recovered |
| 116 | 5/10/27 | 44 | M | 0 | 2 | 3 | 0 | 25 | 18.7 | + | 5.1 | .. | 80 | 72 | Latent syphilis, jaundice |
| | 5/13/27 | .. | .. | .. | 3 | .. | .. | .. | 19.3 | + | .... | .. | 76 | 76 | Increasing jaundice |
| | 5/16/27 | .. | .. | .. | 4 | .. | .. | 21 | 21.7 | + | 7.3 | .. | 76 | 76 | Duodenal drainage; no result |
| | 5/18/27 | .. | .. | .. | 4 | .. | .. | 18 | 23.4 | + | .... | .. | 76 | 76 | Maximal jaundice |
| | 5/20/27 | .. | .. | .. | 4 | .. | .. | 30 | 21.2 | + | .... | .. | 76 | 70 | Duodenal drainage; good result |
| | 5/23/27 | .. | .. | .. | 3 | .. | .. | 21 | 18.3 | + | 5.4 | .. | 60 | 60 | Duodenal drainage; good result |
| | 5/25/27 | .. | .. | .. | 1 | .. | .. | 23 | 13.5 | + | 4.7 | .. | 64 | 60 | |
| | 5/28/27 | .. | .. | .. | 2 | .. | .. | 21 | 9.9 | + | 6.5 | .. | 56 | 40 | Decreasing jaundice |
| | 5/31/27 | .. | .. | .. | 1 | .. | .. | 22 | 8.4 | + | 5.5 | .. | 56 | 56 | Dismissed from hospital |
| | 1/10/28 | .. | .. | .. | 0 | .. | .. | 29 | 0.2 | 0 | 4.5 | .. | 8 | 2 | Eight months later recovered |
| 117 | 11/16/26 | 48 | M | 0 | 2 | 1 | 0 | .. | 15.8 | + | .... | .. | 80 | 72 | Latent syphilis, jaundice |
| | 11/18/26 | .. | .. | .. | 4 | . | .. | 38 | 21.4 | + | .... | .. | 64 | 60 | Increasing jaundice |
| | 11/21/26 | .. | . | .. | 4 | .. | .. | 10 | 17.6 | + | 6.4 | .. | 80 | 72 | |
| | 11/25/26 | .. | .. | .. | 3 | .. | .. | .. | 15.6 | + | .... | .. | 80 | 75 | |
| | 11/28/26 | .. | .. | .. | 4 | .. | .. | 42 | 18.7 | + | 5.5 | .. | 82 | 80 | Condition stationary |
| | 12/ 2/26 | .. | .. | .. | 4 | .. | .. | .. | 20.5 | + | .... | .. | 80 | 80 | |
| | 12/ 5/26 | .. | .. | .. | 4 | .. | .. | .. | 20.6 | + | .... | .. | 80 | 80 | |
| | 12/ 9/26 | .. | .. | . | 3 | .. | .. | .. | 16.5 | + | 5.1 | .. | 90 | 80 | Decreasing jaundice |
| | 12/12/26 | .. | .. | .. | 3 | .. | .. | .. | 9.0 | + | .... | .. | 80 | 75 | |
| | 12/14/26 | .. | .. | .. | 2 | .. | .. | .. | 11.4 | + | .... | .. | .. | .. | Dismissed from hospital |
| 118 | 7/21/28 | 41 | M | 1 | 4 | 4 | 0 | .. | 34.8 | + | .... | .. | 96 | 80 | Latent syphilis; jaundice |
| | 7/25/28 | .. | .. | .. | 3 | .. | .. | 35 | 19.0 | + | .... | .. | 96 | 80 | Decreasing jaundice with duodenal drainage |
| | 7/30/28 | .. | .. | .. | 2 | .. | .. | .. | 13.6 | + | .... | .. | .. | .. | |
| | 8/ 9/28 | .. | .. | .. | 1 | .. | .. | 27 | 2.8 | + | .... | .. | 34 | 16 | Recovering |
| 119 | 2/ 1/28 | 45 | M | .. | 3 | 2 | .. | .. | 17.3 | + | 7.4 | .. | 72 | 60 | Neurosyphilis; jaundice |
| | 2/15/28 | .. | .. | .. | 1 | . | .. | 30 | 2.0 | + | 4.9 | .. | 20 | 8 | Recovering |
| 120 | 1/22/27 | 56 | M | .. | 3 | 1 | .. | 18 | 5.0 | + | 7.8 | .. | 100 | 66 | Neurosyphilis; jaundice |
| | 3/ 2/27 | .. | .. | .. | 0 | .. | .. | 16 | 1.3 | 0 | 4.7 | .. | 6 | 2 | Recovery |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 121 | 7/27/27 | 48 | M | 3 | 2 | 1 | 0 | .. | 10.7 | + | ... | .. | .. | .. | Latent syphilis; jaundice |
| | 8/ 3/27 | .. | .. | .. | 3 | .. | .. | .. | 22.1 | + | ... | .. | .. | .. | Maximal jaundice |
| | 8/11/27 | .. | .. | .. | 3 | .. | .. | .. | 14.7 | + | ... | .. | .. | .. | Improving |
| | 8/19/27 | .. | .. | .. | 2 | .. | .. | .. | 4.3 | + | ... | .. | .. | .. | |
| | 9/ 6/27 | .. | .. | 3 | .. | .. | 0 | 18 | 1.4 | + | ... | .. | 8 | 4 | |
| | 1/31/28 | .. | .. | .. | 0 | .. | .. | 18 | 0.6 | 0 | 4.9 | .. | 2 | 0 | Recovery 5 months later |
| | 8/30/28 | .. | .. | .. | 0 | .. | .. | 20 | 0.2 | 0 | ... | .. | 6 | 0 | |
| 122 | 3/29/28 | 42 | M | + | 1 | 1 | .. | 22 | 6.7 | + | ... | .. | 80 | 72 | Neurosyphilis; jaundice |
| | 4/ 4/28 | .. | .. | + | 2 | .. | .. | 13 | 7.8 | + | ... | .. | 80 | 60 | Improvement with duodenal drainage |
| | 4/11/28 | .. | .. | .. | .. | .. | .. | 14 | 2.4 | + | ... | .. | .. | .. | |
| | 6/ 1/28 | .. | .. | .. | .. | .. | .. | .. | 0.2 | ± | ... | .. | 10 | 2 | Recovery |
| 123 | 5/ 4/27 | 25 | M | .. | .. | .. | .. | 12 | 7.0 | + | 5.5 | .. | 44 | 38 | Mucous patches; jaundice increasing; recovery later |
| | 5/ 6/27 | .. | .. | .. | 2 | .. | .. | .. | 15.0 | + | 8.1 | .. | 80 | 72 | |
| 124 | 4/ 2/27 | 47 | M | 0 | 2 | 1 | .. | 33 | 7.0 | + | 6.5 | .. | 64 | 64 | Tabes; jaundice |
| | 4/ 4/27 | .. | .. | .. | .. | .. | .. | 31 | 7.0 | + | 8.1 | .. | 76 | 76 | |
| | 4/ 6/27 | .. | .. | .. | .. | .. | .. | 27 | 6.8 | + | 6.2 | .. | 72 | 64 | |
| 125 | 5/25/28 | 39 | M | 0 | 2 | 4 | 0 | .. | 5.3 | + | ... | .. | 80 | 66 | Neurosyphilis; jaundice |
| | 6/ 4/28 | .. | .. | .. | .. | .. | .. | .. | 3.9 | + | ... | .. | .. | .. | Improving with treatment |
| | 6/ 9/28 | .. | .. | .. | 1 | .. | .. | 31 | 1.7 | + | ... | .. | 12 | .. | |
| | 7/ 9/28 | .. | .. | .. | 0 | .. | .. | 26 | 0.8 | + | ... | .. | 12 | 0 | Recovery |
| 126 | 1/12/28 | 50 | M | + | 2 | 4 | 0 | 18 | 3.4 | + | 5.3 | .. | 40 | 38 | Neurosyphilis; jaundice |
| | 1/24/28 | .. | .. | .. | .. | .. | .. | 17 | 3.6 | + | 4.7 | .. | 60 | 40 | Improving |
| | 2/ 2/28 | .. | .. | .. | .. | .. | .. | .. | 1.4 | + | 5.0 | .. | .. | 6 | Recovery |
| 127 | 2/11/28 | 49 | M | .. | .. | .. | .. | 61 | 5.1 | + | 6.1 | .. | 40 | 36 | Neurosyphilis; jaundice |
| | 2/15/28 | .. | .. | .. | .. | .. | .. | .. | 3.7 | + | 5.7 | .. | 56 | 40 | Improving |
| | 2/21/28 | .. | .. | .. | .. | .. | .. | 29 | 1.7 | + | 5.4 | .. | 44 | 34 | |
| | 2/23/28 | .. | .. | .. | .. | .. | .. | 45 | 1.4 | + | ... | .. | 40 | 29 | |
| | 3/ 9/28 | .. | .. | .. | .. | .. | .. | 35 | 1.4 | ± | ... | .. | 24 | 6 | Recovery |
| 128 | 8/ 2/27 | 41 | M | 0 | 1 | .. | 0 | .. | 6.2 | + | ... | .. | 50 | 20 | Latent syphilis; jaundice |
| 129 | 7/ 1/26 | 36 | M | 0 | 2 | 4 | .. | 54 | 5.6 | + | 2.7 | .. | 36 | 28 | Neurosyphilis; jaundice |
| 130 | 8/ 7/26 | 32 | M | 1 | 2 | 4 | .. | .. | 4.3 | + | 5.8 | .. | 50 | 44 | Neurosyphilis; jaundice; improving |
| 131 | 12/ 7/25 | 52 | M | 3 | 1 | 12 | 0 | 22 | 1.8 | + | 2.7 | 50 | 36 | 28 | Neurosyphilis; jaundice clearing |
| 132 | 4/15/25 | 40 | M | 0 | 2 | 4 | 0 | 7 | 3.7 | + | ... | 40 | 15 | 7 | Latent syphilis; jaundice clearing |
| 133 | 2/ 1/27 | 29 | M | .. | 0 | .. | 0 | 30 | 1.5 | 0 | 5.0 | .. | 2 | 0 | Recovered from jaundice 5 months before |

sodium thiosulphate with duodenal drainage on alternate days. There was little change the first week. The jaundice deepened slightly, and the serum bilirubin increased to 23.4 mg. Only a small amount of bile-stained fluid was obtained by duodenal drainage at this time.[20] The quantity of material obtained gradually increased, and a good flow of bile was secured at the last three drainages. The jaundice began to disappear at that time, and thereafter recovery was uninterrupted. The patient was only slightly jaundiced when he was dismissed from observation on May 31, and he was entirely well when last seen in January, 1928.

This case, clinically, was one of mild postarsphenamine jaundice with complete recovery. The laboratory studies were of interest because it was possible to follow the changes during both the periods of development and of recession of the jaundice. This curve was accurately pictured by the changes in the serum bilirubin. The case was a good demonstration of the value of determining the serum bilirubin content in following the course of a case of jaundice, for the changes were much more clear cut than those in the skin or mucous membranes. A direct van den Bergh reaction was obtained during the course of the jaundice. There was no change in the bile acid content of the blood. There was marked retention of bromsulphalein during the period of jaundice. The degree of dye retention decreased slowly, but persisted for a considerable period after the disappearance of the bilirubinemia. When the patient was last examined in January, 1928, normal readings were obtained with all tests.

Case 89 (table 7).—A man, aged 60, came to the clinic in May, 1924, when he was found to have parenchymatous and meningeal neurosyphilis. He was given six intravenous injections of arsphenamine for a total of 2.2 Gm. in conjunction with thirty intramuscular injections of succinimide of mercury and twenty-seven intravenous injections of sodium iodide. This course of treatment was completed about the middle of July, and the patient was sent home with directions to take mercurial inunctions. He returned to our care September 17 because of painless jaundice of two weeks' duration. The serum bilirubin content at that time was 5.6 mg. in each 100 cc. The jaundice, which was associated with light-colored stools and dark urine, gradually progressed. He had lost his appetite, and experienced a marked sense of fatigue and exhaustion, and severe pains in the leg and arm, associated with slight paresthesia of the lower extremities.

Duodenal lavage was unsatisfactory. The increase in the degree of jaundice, and the associated prostration and evidences of toxicity, led us to believe that the patient had toxic hepatitis. As is customary in these cases, there was great irritability of the kidney. The patient remained in the hospital approximately three months and received twenty-one additional injections of succinimide of mercury. Peripheral neuritis was extremely troublesome, and cord bladder necessitated daily irrigation during this time. The jaundice persisted for four months but finally cleared up completely. At the time of dismissal of this patient, a diagnosis was made of toxic hepatitis due either to syphilis or to arsenic. It was approximately a year before the neuritis and the edema of the extremities disappeared, and the patient again began to feel well.

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20. Wilhelm, L. F. X.: Duodenal Lavage in the Treatment of Jaundice Complicating the Treatment for Syphilis, Arch. Dermat. & Syph. **10**:499 (Oct.) 1924.

This case was of particular interest because it was possible to follow the changes during the development of jaundice. The serum bilirubin increased progressively from 5.6 to 20 mg. in each 100 cc. during this period. A maximal degree of dye retention was attained early, and there was relatively little further increase. It was not possible to follow the curve of recovery, but six weeks later the bilirubin and phenoltetrachlorphthalein readings had returned to normal, although the direct van den Bergh reaction persisted.

### ICTERUS GRAVIS

Acute yellow atrophy or icterus gravis may develop as a result of many conditions. Taken by itself it is not characteristic of syphilis, although it occasionally is syphilitic in origin. Many of the reported cases have been described in association with acute secondary syphilis. There is no sharp line of distinction, other than the acuteness and severity, between this condition and the acute syphilitic hepatitis previously described. Similarly, the hepatic injury producing arsphenamine

TABLE 8 (case 134).—*Illustrative Case of Acute Yellow Atrophy*

| Date | Blood Urea, Mg. for Each 100 Cc. | Blood Creatinine, Mg. for Each 100 Cc. | Phenoltetrachlorphthalein Test: Dye in Serum, per Cent | | |
|---|---|---|---|---|---|
| | | | 15 Minutes | 30 Minutes | 60 Minutes |
| 9/14/23..... | 184 | 3.8 | 34 | 30 | 24 |

jaundice usually is of moderate severity, and the patient readily recovers. In some cases, however, there is an overwhelming injury to the hepatic parenchyma. Such cases may well be classified as acute yellow atrophy. The history of an illustrative case follows.

CASE 134 (table 8).—A man, aged 38, came to the clinic in January, 1923, because of jaundice associated with weakness and malaise. The jaundice had been present about ten days at the time of his admission; also, the lassitude and the loss of appetite had been noted for about two weeks. The stools were clay-colored. The patient had had a definite dull pain in the hepatic region for several weeks preceding the onset of the jaundice. On examination, the Wassermann reaction of the blood was found to be strongly positive, and he gave a definite history of syphilis of twenty years' duration. The liver and the spleen were both greatly enlarged, extending almost to the umbilicus. Antisyphilitic treatment was started, using mercury with chalk by mouth and small doses of potassium iodide. Abdominal pain, which increased steadily for a period of several weeks, necessitated the discontinuance of all treatment. Following this, there was gradual recession in the jaundice and apparent improvement in the patient's general condition. One month after the mercury by mouth had been started, the patient received his first small injection of neoarsphenamine, 0.2 Gm., and in eight days the same dose was repeated. He was sent home the latter part of March somewhat improved.

The patient returned to the clinic in August, however, markedly jaundiced. He said that he had been free from jaundice during April and May but that it

had returned the first of July. Since then he had become progressively worse. It is to be noted that while at home he had been given a series of injections of arsphenamine shortly before the recurrence of the jaundice. He was readmitted to the hospital on Aug. 14, 1923. At that time he was markedly jaundiced, and the liver and spleen were enlarged. The Wassermann reaction of the blood was still strongly positive, graded 44. The urine contained much bile and a moderate amount of albumin, but the blood urea content was 16 mg. in each 100 cc. It was felt at this time that he was showing evidence of a Herxheimer effect in syphilitic hepatitis and splenitis. The routine therapeutic measures were unavailing, and his condition became rapidly worse. Edema of the legs and abdominal ascites developed, and paracentesis by which 1,600 cc. was obtained was done on September 3. The fluid recurred rapidly so that it was impossible to follow changes in the size of the liver which, however, seemed to decrease somewhat. Later there was profuse oozing of blood from the mouth and nose, and still later from the bowel, while the blood urea content rose from 26 to 184. The patient was profoundly toxic the greater portion of the time. Later he became stuporous and was in a state of coma during the last few days of his life. He died on September 15.

Postmortem examination revealed destructive hepatitis and splenitis. The liver weighed 978 Gm. and the spleen, 546 Gm., and the pathologist considered the condition of both to be syphilitic. There was also acute diffuse nephritis.

Laboratory studies were made the day before death. The serum bilirubin was elevated, but a quantitative estimation was not made. A direct van den Bergh reaction was present, and there was marked retention of phenoltetrachlorphthalein. The most striking change was the terminal rise in the blood urea content during the last week of life.

Stadie and Van Slyke [21] and others reported cases of acute yellow atrophy in which there was increase in the amino-acid content of the blood but in which the urea content was normal. The same content of the blood in jaundice is almost pathognomonic for acute yellow atrophy, but we wish to emphasize the fact that there are many cases of icterus gravis in which this particular type of disturbance in the chemical composition of the blood does not occur. The case cited is an example.

### HEPATIC RECURRENCE AND HERXHEIMER EFFECT IN THE LIVER

Syphilologists have recognized since the advent of arsphenamine two therapeutic effects: the Herxheimer reaction, and the recidive or "recurrence." An outstanding example of the Herxheimer reaction, or therapeutic shock, is observed clinically following the administration of a dose of arsphenamine to a patient with an acute syphilitic roseola. Within twenty-four hours following the injection there is marked accentuation of the cutaneous syphilid, and as a rule there are constitutional signs such as fever and malaise. The clinical evidence of recur-

21. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. **25**:693 (June) 1920.

rence is most readily observed in patients with acute syphilis who are inadequately treated. One or two injections of arsphenamine, not accompanied by mercury or bismuth, frequently result in the reappearance of the active syphilitic lesions. The same process may take place in the liver, and the following case report is offered as an example of diffuse syphilitic hepatitis or a "hepato-recurrence" which developed in a patient who was inadequately treated for acute syphilis.

CASE 135 (table 9).—A patient, aged 37, had had a penile chancre in June, 1926. He received three intravenous injections of arsphenamine at five day intervals at that time but did not receive mercury. Five days after the last injection he became jaundiced. This jaundice persisted, although it varied somewhat in intensity from day to day. The stools were clay-colored, and pruritus was

TABLE 9 (case 135).—*Progress in an Illustrative Case of Hepato-Recurrence and Herxheimer Effect in the Liver*

| Date | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test: Dye in Serum, per Cent | | |
|---|---|---|---|---|---|---|---|
| | | | | | 15 Minutes | 30 Minutes | 60 Minutes |
| 1/31/27 | .. | 21.4 | + | .... | .. | .. | .. |
| 2/14/27 | 36 | 35.0 | + | 11.5 | .. | 72 | 40 |
| 2/17/27 | 39 | 31.6 | + | 11.0 | .. | 72 | 40 |
| 2/19/27 | .. | 27.3 | + | ... | .. | .. | .. |
| 2/21/27 | .. | 25.9 | + | ... | .. | .. | .. |
| 2/23/27 | .. | 22.4 | + | ... | .. | .. | .. |
| 2/24/27 | 22 | 27.8 | + | ... | .. | 72 | 60 |
| 2/26/27 | .. | 20.0 | + | ... | .. | .. | .. |
| 2/28/27 | 32 | 14.3 | + | 7.5 | .. | 72 | 72 |
| 3/ 2/27 | 50 | 14.2 | + | 6.8 | .. | 68 | 60 |
| 3/ 4/27 | .. | 10.2 | + | ... | .. | .. | .. |
| 3/ 7/27 | .. | 10.4 | + | ... | .. | 72 | 68 |
| 3/11/27 | .. | 9.1 | + | 3.9 | .. | 72 | 40 |
| 3/14/27 | 27 | 8.5 | + | ... | .. | 72 | 40 |
| 3/17/27 | 18 | 6.2 | + | 5.3 | .. | 72 | 40 |
| 3/21/27 | 32 | 5.3 | + | ... | .. | 60 | 44 |
| 3/24/27 | 19 | 5.9 | + | 3.8 | .. | 72 | 64 |
| 5/27/27 | .. | 0.5 | 0 | ... | .. | 12 | 12 |

marked. There was no gastro-intestinal disturbance, but he lost 35 pounds (15.9 Kg.) in weight. He was admitted to the clinic on Jan. 30, 1927, five months after the appearance of the jaundice. He was moderately icteric; the serum bilirubin content was 21.4 mg. in each 100 cc. The edge of the liver was palpable below the costal margin. The Kolmer modification of the Wassermann reaction performed on the blood was negative, but the reaction to the Kahn test was positive.

A moderate amount of bile-stained fluid was obtained on duodenal drainage but the jaundice persisted, the serum bilirubin content fluctuating between 22.4 and 35.0 mg. The patient was given dextrose intravenously for two weeks in addition to the lavages, but without improvement. On February 18, the daily intramuscular injection of succinimide of mercury in 1/6 grain (0.0108 Gm.) doses was started. This was supplemented by potassium iodide. He made a steady and uneventful convalescence under this regimen and was dismissed from the hospital on March 22. He was still slightly jaundiced, and the serum bilirubin content was 5.3 mg. at that time. Two months later the jaundice had completely disappeared, and the serum bilirubin content was 0.5 mg. The edge of the liver was just palpable. He has remained well since then.

The laboratory studies in this case extend over the major portion of time during which the patient was suffering from an attack of jaundice. There was an initial rise in the serum bilirubin from 21.4 to 35.0 mg. in each 100 cc. during the development of the jaundice. The bilirubin content in the blood gradually subsided during the period of recovery and had fallen to 5.9 mg. when the patient was dismissed on March 24. A direct van den Bergh reaction was obtained during this period. When the patient was seen two months later the serum bilirubin was normal, and the van den Bergh reaction was indirect. The Pettenkofer test showed an increase in the bile acids in the blood at the height of the jaundice. This rapidly disappeared as the clinical condition improved. The bromsulphalein test, on the other hand, showed a maximal retention of dye when the patient first was seen, and this persisted throughout his stay in the hospital. When last seen he still showed moderate retention of bromsulphalein. Unfortunately, it was not possible to examine him at a later date to determine whether there was an eventual return to normal. This case again is an illustration of the value of the determination of the serum bilirubin content in following the course of a case of jaundice.

### TREATMENT CIRRHOSIS

We have stressed the danger of too vigorous therapeutic measures in the presence of hepatic syphilis. Arsphenamine in particular should be used with caution. This is particularly true because of the insidious character of the injury to the liver produced by arsenic. Much evidence has been accumulated to show that considerable destruction of hepatic tissue may take place without there being any accompanying jaundice or other recognizable clinical symptoms. Fibrous tissue proliferation follows, and with repeated hepatic injury cirrhosis develops. O'Leary, Snell and Bannick [22] reported two cases of portal cirrhosis apparently resulting from the long-continued use of inorganic arsenic as the solution of potassium arsenite. We present the history of a case in which it seemingly followed the use of arsphenamine. This patient, as far as could be judged, was free from syphilis so that the cirrhosis is most readily ascribed to the action of arsphenamine.

CASE 136 (table 10).—The patient first came to the clinic in 1916, when he complained of numbness in the right arm and shoulder. Neurologic examination suggested the possibility of syphilis, and it apparently was confirmed at that time by a weakly positive Wassermann reaction of the blood. During the next five years, he received a series of eighteen intravenous injections of arsphenamine for a total of 7.9 Gm., 200 mercurial inunctions and approximately thirty-six intra-

22. O'Leary, P. A.; Snell, A. M., and Bannick, E. G.: Portal Cirrhosis Associated with Chronic Inorganic Arsenical Poisoning: Report of Two Cases, J. A. M. A. **90**:1856 (June 9) 1928.

muscular injections of succinimide of mercury. The patient was always greatly concerned about the syphilis, and although repeated examinations of the spinal fluid and blood tests following the original course of treatment were all negative, he took further treatment from time to time from other physicians, against our advice. He was seen almost annually, but no further evidence of syphilis was obtained.

In May, 1926, the patient began to have some abdominal pain and enlargement of the abdomen. Walking or jarring materially aggravated the discomfort. Ten days after the onset of this abdominal discomfort, it was noted that he had fluid in the abdomen. He returned to the clinic on May 14, 1926. The skin had a subicteric tint, and there was moderate abdominal distention. The liver and spleen were not palpable. The serum bilirubin content was 4.4 mg. in each 100 cc. He was treated with diuretics in the form of ammonium chloride and merbaphen with marked success. At the time of his dismissal, the latter part of June, he had lost 36 pounds (16.3 Kg.) and was entirely free from ascites. The liver and spleen were just palpable at the costal margin. He remained well at home but returned to the clinic in August of the same year, for reexamination. There was

TABLE 10 (case 136).—*Progress in an Illustrative Case of Treatment Cirrhosis, in a Nonsyphilitic Patient*

| Date | Blood Urea, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test; Dye in Serum, per Cent | | |
|---|---|---|---|---|---|---|---|
| | | | | | 15 Minutes | 30 Minutes | 60 Minutes |
| 5/17/23 | 24 | 4.4 | + | 4.4 | 100 | 72 | 54 |
| 5/24/23 | 49 | 2.8 | + | ... | 75 | 54 | 36 |
| 6/ 8/26 | 29 | 3.2 | + | ... | 90 | 82 | 54 |
| 6/15/26 | 32 | 2.7 | + | ... | .. | .. | .. |
| 8/28/26 | 23 | 2.4 | + | ... | .. | 40 | 15 |

no evidence of jaundice, the spleen was definitely palpable and the edge of the liver, smooth and firm, could be felt across the right costal border. Ascites was not demonstrated. The serum bilirubin content was 2.4 mg.

The patient was well for a time but returned in October and was admitted in a state of collapse. He died in about twelve hours from a ruptured esophageal varix. Postmortem examination showed a cirrhotic liver considerably reduced in size and a spleen which was four times its normal size. The ruptured esophageal varix, with evidence of gastro-intestinal hemorrhage, was readily demonstrated.

A series of five readings was made on this patient during the three months period between May 17 and Aug. 28, 1926. Slight bilirubinemia, a direct van den Bergh reaction and marked retention of dye were uniformly present. These observations are identical with those in the cases of syphilitic cirrhosis previously discussed, and in the cases of portal cirrhosis which we have previously reported.

A history of alcoholism was not present in this case, and the pathologists could not find anything at necropsy to indicate that the hepatic cirrhosis was of syphilitic origin, although a stain for spirochetes was not made. Clinical data elicited during the long period of observation were not of help in arriving at a decision as to the cause of the cirrhosis.

We believe, however, that the use of arsphenamine must be considered an etiologic factor and that this is a true case of treatment cirrhosis in a nonsyphilitic patient.

### JAUNDICE ASSOCIATED WITH MALARIA INOCULATION

The introduction by Wagner-Jauregg of inoculation with malaria as a method of treating neurosyphilis marks an undoubted advance in the treatment for syphilis. O'Leary [23] recently reported in detail his clinical experience with this treatment. Of the 400 patients treated by this method, jaundice of varying degree was observed in about 6 per cent. This is of particular interest, for involvement of the liver in malaria has been recognized since the time of Hippocrates. Cirrhosis is the most common condition of the liver in chronic malaria. This, for the most part, is associated with destruction of erythrocytes and usually is spoken of as belonging to the group of types of pigment cirrhosis rather than to the usual type of portal cirrhosis, although Hance [24] thought it should be classified in the latter group. At the same time, it must be kept in mind that some authorities, as MacCallum,[25] have not considered the relationship of malaria and hepatic cirrhosis as wholly established. Jaundice occasionally is seen in malaria, but it must be admitted that the so-called "bilious" form of malaria is one of the rarer manifestations of that disease.

The etiology of the icterus which accompanies the treatment for neurosyphilis by malaria is difficult to establish. The same situation exists here as is found in the so-called postarsphenamine jaundice. It is recognized that direct action of malaria on the liver, activation of syphilitic hepatitis or some other secondary infectious agent may be at fault. For the present, this must remain an open question. Herewith are the history and results of laboratory examination in an illustrative case.

CASE 137 (table 11).—A dentist, aged 34, first came to the clinic in June, 1925, because of an early case of syphilis of the central nervous system. He had been treated with arsphenamine by his local physician, and when he was examined at the clinic the Wassermann reaction of the blood was negative but that of the spinal fluid was positive. During the next eighteen months he had two further courses of arsphenamine, supplemented by a course of intraspinal treatment according to the Swift-Ellis-Ogilivie technic without a change in the reaction of the spinal fluid.

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23. O'Leary, P. A.: Treatment of Neurosyphilis by Malaria: Serologic Results and a Comparison with Treatment by Typhoid Vaccine, J. A. M. A. **91**:543 (Aug. 25) 1928.

24. Hance, J. B.: On Malaria as an Independent Etiological Factor in Portal Cirrhosis, Guy's Hosp. Rep. **78**:379, 1928.

25. MacCallum, W. G.: A Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 1162.

TABLE 11.—*Jaundice Associated with Malaria Inoculation*

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice, Graded 0 to 4 | Spleen Enlarged | Hemoglobin Content | Erythrocytes, Millions | Leukocytes | Blood Urea, Mg. for Each 100 Cc. | Blood Uric Acid, Mg. for Each 100 Cc. | Serum Bilirubin, Mg. for Each 100 Cc. | Van den Bergh Direct Reaction | Bile Acids, Mg. for Each 100 Cc. of Blood | Bromsulphalein Test: Dye in Serum, per Cent 15 Min. | 30 Min. | 60 Min. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 137 | 12/ 9/26 | 35 | M | 0 | 0 | 0 | 77 | 4.68 | 8,000 | 18 | 2.7 | ... | 0 | ... | .. | .. | .. | Neurosyphilis; malaria inoculation |
| | 12/21/26 | .. | .. | 0 | 2 | + | 55 | 2.95 | 7,800 | 72 | 5.7 | 6.6 | + | ... | .. | 36 | 36 | After 10 chills |
| 138 | 3/25/27 | 50 | M | 0 | 0 | 0 | 73 | 4.41 | 7,100 | 30 | 2.0 | ... | .. | ... | .. | .. | .. | Neurosyphilis; malaria inoculation |
| | 4/ 5/27 | .. | .. | 0 | 1 | 0 | 60 | 3.57 | 7,000 | 39 | 2.4 | 6.8 | + | 5.6 | .. | 60 | 40 | After 4 chills |
| | 4/ 7/27 | .. | .. | 0 | 2 | 0 | .. | .... | ..... | 21 | 2.5 | 8.2 | + | 5.4 | .. | 75 | 60 | Quinine given |
| | 4/11/27 | .. | .. | 0 | 1 | 0 | 60 | 3.48 | 7,400 | 17 | 2.2 | 4.4 | + | 4.7 | .. | 60 | 60 | |
| | 4/18/27 | .. | .. | 0 | 1 | 0 | 55 | 3.40 | 8,000 | 25 | ... | 3.3 | + | 3.6 | .. | 40 | 36 | Recovering |
| 139 | 1/13/27 | 42 | M | 0 | 0 | 0 | 75 | 4.36 | 7,600 | 16 | 2.9 | ... | .. | ... | .. | .. | .. | Neurosyphilis; malaria inoculation |
| | 1/24/27 | .. | .. | 0 | 1 | 0 | 55 | 3.21 | 2,900 | 70 | 5.3 | 3.0 | + | ... | .. | 30 | 20 | After 9 chills |
| 140 | 7/15/26 | 45 | M | 0 | 0 | 0 | 72 | 4.59 | 4,100 | .. | ... | ... | .. | ... | .. | .. | .. | Neurosyphilis; malaria inoculation |
| | 7/26/26 | .. | .. | 2 | 2 | + | .. | .... | ..... | 36 | 3.6 | 23.4 | + | 5.6 | .. | 80 | 80 | After 4 chills |
| | 2/23/27 | .. | .. | 0 | 0 | .. | .. | .... | ..... | .. | ... | 0.6 | 0 | 6.6 | .. | 4 | 0 | Seven months later, recovered |
| 141 | 5/20/27 | 36 | M | 0 | 0 | 0 | 73 | 4.60 | 6,800 | 18 | 2.4 | ... | .. | ... | .. | .. | .. | Neurosyphilis; malaria inoculation |
| | 6/ 4/27 | .. | .. | 0 | 1 | 0 | 70 | 4.31 | 6,500 | 28 | 2.3 | 3.0 | + | 5.5 | .. | 24 | 20 | After 2 chills |
| | 6/20/27 | .. | .. | 0 | 1 | 0 | 50 | 2.70 | 5,000 | 16 | 3.2 | ... | .. | ... | .. | .. | .. | After 10 chills |
| 142 | 4/21/28 | 29 | F | 0 | 0 | 0 | 81 | 4.14 | 8,000 | 20 | 3.4 | ... | .. | ... | .. | .. | .. | Neurosyphilis; malaria inoculation |
| | 5/ 5/28 | .. | .. | 0 | 1 | + | 50 | 2.77 | 4,000 | 30 | 4.9 | 4.7 | + | ... | .. | 30 | 20 | After 4 chills |

Inoculation with malaria was given on Dec. 2, 1926. The first chill occurred four days later. Quotidian chills occurred during the next ten days. There was slight conjunctival icterus on December 14, which progressively increased. Enlargement of the spleen could first be demonstrated on December 20. The patient had ten chills by December 22. There was moderate jaundice, and the spleen was readily palpable. Quinine was then administered, and there was a cessation of the chills and rapid disappearance of other symptoms. Three days later the spleen was no longer palpable, and the jaundice had markedly decreased.

Anemia developed rapidly with a marked fall in both the hemoglobin content and the erythrocyte counts, but the leukocyte count was unchanged. The urinary output was more than 1,000 cc. daily, but the blood urea content rose progressively from 18 to 72 mg. in each 100 cc., and the uric acid from 2.7 to 5.7 mg. in each 100 cc. Marked jaundice developed with a serum bilirubin content of 6.6 mg. in each 100 cc. and a direct van den Bergh reaction. There was retention of bromsulphalein as well.

The changes observed in this patient are characteristic and serve to illustrate those seen in the group as a whole. There are several possible explanations of the changes in the blood. The production of anemia, with the associated appearance of jaundice, suggests a hemolytic crisis in consequence of a destruction of erythrocytes by plasmodial invasion. To that extent the changes may be compared with the similar hemolytic crisis produced by the therapeutic administration of phenylhydrazine in cases of polycythemia vera. The changes in the latter have been reported by Greene and Conner [26] and more recently by Huffman.[27] Huffman found that during therapeutic use of phenylhydrazine there was rapid production of anemia. As the hemoglobin of the destroyed erythrocytes was broken down, the pigment moiety was excreted in the bile as bilirubin, and the protein fractions appeared in the urine as urea. Practically all the destroyed blood could be accounted for in this way. Because of the rapidity of blood destruction, the eliminative facilities of the body were temporarily embarrassed. In consequence, there was transitory increase in the blood urea and serum bilirubin, with consequent jaundice. Apart from this there was little metabolic disturbance, and recovery was rapid and complete.

A similar hemolytic crisis will expain many of the changes in the jaundice following inoculation with malaria. The anemia, jaundice, enlargement of the spleen, bilirubinemia and increase in the blood urea may all be explained on this basis. This view is apparently held by Stitt.[28] Simple hemolysis, however, will not explain all the changes

26. Greene, C. H., and Conner, H. M.: Diseases of the Liver: V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, Arch. Int. Med. **38**:167 (Aug.) 1926.

27. Huffman, L. D.: Metabolic Studies in the Treatment of Polycythemia Vera with Phenylhydrazine, Arch. Int. Med. **39**:656 (May) 1927.

28. Stitt, E. R.: The Diagnosis and Treatment of Tropical Diseases, Philadelphia, P. Blakiston's Son & Company, 1929, pp. 33, 34, 45, 48 and 63.

present. Hemolytic icterus and the jaundice following treatment with phenylhydrazine are characterized by the presence of an indirect van den Bergh reaction and normal values for the bromsulphalein test. Retention of dye and a direct van den Bergh reaction were uniformly present in the cases of jaundice accompanying malaria. These changes can be taken as direct evidence of some degree of hepatic injury, however slight. Likewise, the increase in the uric acid content of the blood is evidence of injury to the tissues and need not be referred exclusively to renal injury. We believe, therefore, that the jaundice associated with inoculation with malaria is not to be considered as due entirely to destruction of blood but must be classified as a hemohepatogenous type of icterus.

### LABORATORY DATA

*Fructose Tolerance.*—Previous experience with the fructose tolerance test in patients with obstructive jaundice or the various types of hepatitis with jaundice was disappointing in contrast to the results of Isaac,[29] Kleeberg,[30] Tachau [31] and others. The changes observed were not sufficiently marked or specific to be of particular diagnostic value. A group of ten patients was subjected to the test in the present series. Only two positive reactions were obtained. Further study did not seem justified, and the test was discarded.

*Nitrogen Partition of the Blood.*—A slight decrease in the blood urea level is found in some of the cases of jaundice observed in this series. The change, however, was always to be explained by reference to the individual case, and usually by the use of diets low in protein and rich in carbohydrate, temporary forcing of the intake of fluids or similar factors. In one case of destructive hepatitis leading to subacute yellow atrophy, the blood urea was normal until just before death, when there was a terminal rise. A similar terminal rise was noted in a case of hepatic gumma and in one of portal cirrhosis. Temporary elevation of the blood urea likewise was noted in the course of several cases of postarsphenamine jaundice, but the administration of large amounts of dextrose and the forcing of fluid in such cases caused a rapid return to normal.

The other nitrogenous constituents of the blood which were studied, the total nonprotein nitrogen, uric acid, creatinine and amino-acid nitrogen did not show characteristic changes.

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29. Isaac, S.: Die klinischen Functionsstörungen der Leber und ihre Diagnose, Ergebn. d. inn. Med. u. Kinderh. **27**:423, 1925.

30. Kleeberg, Ludwig: Über Leberfunktionsprüfungen bei Lues, Med. Klin. **2**:1162, 1920.

31. Tachau, P.: Untersuchungen über die Funktion der Leber bei Lues, unter besonderer Berücksichtigung des Ikterus syphiliticus praecox und der Leberstörungen durch Salvarsan, Dermat. Ztschr. **32**:305, 1921.

*Bile Pigments.*—The value of the serum bilirubin test as a means of following the progress of a case of jaundice is too well recognized to require special emphasis.[32] The results in this series are in entire agreement with the observations made in the other varieties of jaundice which have been studied and reported from this clinic. The estimation of the serum bilirubin offers a more sensitive index to daily changes in the degree of jaundice than the color of the skin or the amount of bile in the urine. The determination of the serum bilirubin content in early cases of toxic hepatitis, or in cases of cirrhosis, has permitted the recognition of latent jaundice before the icterus became manifest clinically. Reference should also be made, particularly in postarsphenamine jaundice, to the disparity observed in some cases between the intensity of the jaundice and the clinical symptoms. During recovery, the two tend to improve together, but at the height of the disease they do not necessarily correspond. This emphasizes the point that a single determination is of less value than a study of the curve of change in the serum bilirubin. The degree of bilirubinemia in the cases of postarsphenamine jaundice was entirely comparable with those observed in the acute hepatitis of nonsyphilitic origin; the maximal value was 32.5 mg. of bilirubin in each 100 cc. Normal values for the serum bilirubin were found in those cases of syphilis in which there was no involvement of the liver and in those of hepatic gumma.

A direct van den Bergh reaction was observed in all the cases of marked jaundice of whatever type. In ordinary usage, we have not found any advantage in following the various reported subgroups of this reaction. The majority of these have been reported as direct in the accompanying tables. In cases of postarsphenamine jaundice we have observed that there may be a slight initial increase in the serum bilirubin, while the serum gives an indirect or delayed direct van den Bergh

32. Chargin, Louis, and Orgel, S. Z.: Jaundice in Syphilitic Persons Receiving Arsenical Medication: Its Early Detection and Possible Prevention, Arch. Dermat. & Syph. **7**:495 (April) 1923. Dixon, H. A.; Campbell, W. R., and Hanna, M. I.: The Control of Arsphenamine Treatment by Liver Function Tests, Canad. M. A. J. **16**:551, 1926. Gerrard, W. I.: The Recognition of Latent Jaundice During Treatment with Arsenobenzol Compounds, Brit. M. J. **2**:224, 1924. Kloeppel, F. W.: Lues und Salvarsan in ihrem ätiologischen Zusammenhang mit Bilirubinämie und Ikterus, Dermat. Ztschr. **37**:137, 1922-1923. Schamberg, J. F., and Brown, Herman: Bilirubin Determinations in the Blood as a Measure of Liver Damage in Treatment with Arsphenamines, J. A. M. A. **82**:1911 (June 14) 1924. Schneider, Paul: Untersuchungen über den Bilirubingehalt des Blutserums bei Salvarsan-Quecksilberkur, Dermat. Wchnschr. **74**:228, 1922. Strauss, L., and Buerkmann, W.: Der Einfluss des Salvarsans auf die Bilirubin-Reaktion im Blutserum bei Lueskranken, zugleich ein Beitrag zur Frage der Salvarsanschädigungen, Klin. Wchnschr. **1**:1407, 1922. Wechselmann and Hohorst, W.: Ueber den Einfluss der Salvarsanbehandlung auf den Bilirubingehalt des Blutserums, Arch. f. Dermat. u. Syph. **136**:285, 1921.

reaction. This changes rapidly, and with further increase in the amount of pigment retained in the blood the reaction becomes direct. Similarly, as the jaundice disappears, a direct or delayed direct reaction may be obtained for several days or even for several weeks after the normal level of bilirubin is regained.

*Dye Retention.*—Phenoltetrachlorphthalein was used to measure the retention of dye in the majority of these cases. In the more recent cases bromsulphalein was used instead. The results were qualitatively alike with the two dyes. Normally they leave the blood at different rates; therefore, the samples of blood must be taken at different times. Because of this it is not possible to compare the two dyes directly or to convert readings obtained with one into readings obtained with the other. However, we have not observed definite retention of phenoltetrachlorphthalein without likewise finding retention of bromsulphalein. Bromsulphalein is somewhat less irritating to the veins than phenoltetrachlorphthalein and so is preferable for repeated use.

Retention of these dyes was observed in all cases of hepatitis with jaundice of whatever type.[33] The changes again are similar to those found in nonsyphilitic cases. The changes in retention of dye are similar to those observed in the serum bilirubin although the return to normal in the retention is greatly delayed. In the majority of the cases of toxic hepatitis or postarsphenamine jaundice, the abnormal retention of dye completely disappeared after recovery, but a slight degree of retention occasionally persisted for a considerable period following recovery and the return of the bilirubin to normal.

The results in general were similar in the various forms of syphilitic hepatitis. In case 6 (table 5), the phenoltetrachlorphthalein reading returned to normal with the clearing up of the initial hepatic lesion. With further progress and the apparent development of cirrhotic changes, abnormal retention of dye again appeared.

The cases of gumma were variable. The majority showed slight degrees of abnormal retention of dye. The readings obtained in the

33. Broun, G. O.: Toxic Hepatitis Following Salvarsan Administration, M. Clin. North America **7**:989, 1923. Epstein, N. N., and Rauschkolb, J. E.: The Rose Bengal Test for Liver Function with Particular Reference to Its Use in the Therapy of Syphilis, Arch. Dermat. & Syph. **14**:122 (Aug.) 1926. Greenbaum, S. S., and Brown, Herman: The Phenoltetrachlorphthalein Liver Test in Cases of Acute and Chronic Syphilis Under Treatment and in Various Skin Diseases, J. A. M. A. **82**:88 (Jan. 12) 1924. Piersol, G. M., and Bockus, H. L.: Comparative Studies in Liver Function by Some of the Later Methods, J. A. M. A. **83**:1043 (Oct. 4) 1924. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests: A Comparative Study, J. A. M. A. **91**:1768 (Dec. 8) 1928. Rosenthal, S. M.: The Phenoltetrachlorphthalein Test for Hepatic Function: Recent Studies with the Author's Method, J. A. M. A. **83**:1049 (Oct. 4) 1924.

different cases varied considerably, depending, perhaps, on both the extent and the severity of the process in the liver. The cases of cirrhosis, on the other hand, were more uniform; practically all showed the presence of a moderate degree of retention. The results of the phenoltetrachlorphthalein and bromsulphalein tests, in such cases, are of greater diagnostic value; for in these, retention of dye occurs without there being a coincident elevation of the serum bilirubin.

*The Bile Acids.*—The study of the bile acid content of the blood by means of the Pettenkofer test was without diagnostic import in this series of cases. In a few cases of syphilitic hepatitis with jaundice, or of postarsphenamine jaundice, there was an increase in bile acids. The increase in the bile acids apparently is transitory and is confined to the acute stage of the disease. The normal level of bile acids is regained much sooner than is that of the serum bilirubin and sooner, also, than the retention of dye becomes normal. The changes in the bile acids, therefore, are similar in character to those found by Snell, Greene and Rowntree [34] in experimental obstructive jaundice. In all but these few cases, the values for the bile acid content of the blood, as given by the Pettenkofer test, were within the usual limits of normal.

## COMMENT

"Syphilis, the great imitator, is perhaps never seen in a more advantageous rôle, as such, than in hepatic disease." [15] The present group of cases well illustrates the applicability of this statement. The different clinical pictures cited, as well as the various accompanying laboratory data, have their counterparts in nonsyphilitic disease. In consequence it is necessary, in a discussion of the hepatic complications of syphilis, to speak not in general terms but in specific terms, not of syphilis of the liver, but of a particular form of hepatic syphilis. Differential diagnosis is difficult, and may require the use of all available information, whether from the history, general examination or laboratory examinations. Such information is essential both for prognosis and for the institution of rational treatment.

This is well illustrated by a comparison of acute syphilitic hepatitis accompanied by jaundice with postarsphenamine jaundice. The differentiation is to be made wholly on the basis of the history and the clinical data. Acute syphilitic hepatitis with jaundice develops independently of treatment and appears in association with, or shortly following, the appearance of the secondary manifestations of acute syphilis. When it is of a mild form, acute hepatitis responds to antisyphilitic measures,

34. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Disease of the Liver: VII. Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. **40**:471 (Oct.) 1927.

but when it is severe it may progress to acute yellow atrophy and death. Postarsphenamine jaundice, on the other hand, develops in a patient who previously has received treatment. The course of the mild case is usually uneventful, and as Wilhelm [21] showed, it responds readily to therapeutic procedures. The severe forms, on the other hand, may go on to acute yellow atrophy, or, if the injury is less acute, a portal type of cirrhosis may be produced. Once the jaundice has developed, the clinical symptoms and the degree of apparent intoxication of the patient are alike in the two types. Then the differences are more of degree, than of kind, and so are not characteristic. In consequence, the differential diagnosis must be made largely on the basis of the history and collateral information. The confusion of postarsphenamine jaundice with the ordinary nonspecific infectious hepatitis likewise has been pointed out, among others, by Stokes, Ruedemann and Lemon.[35]

The changes in the functional tests in these forms of acute hepatitis are indistinguishable. The most useful of the criteria available for showing the development and intensity of hepatitis following the administration of arsphenamine is the determination of bilirubin. An increase in the serum bilirubin precedes the first sign of incipient or developing icterus, a point to which numerous authors have called attention. Similarly, decrease in the serum pigment and return of the bilirubin to the normal level precedes the disappearance of the icterus in the skin and mucous membranes. The dyes, whether phenoltetrachlorphthalein or bromsulphalein, are retained in a fashion similar to the retention of bilirubin, although the fluctuations with the course of the disease are not so marked, and the return to normal is not so rapid as in the case of the bilirubin. Because of the greater sensitivity to daily fluctuations and ease of the procedure, determination of the bilirubin content is somewhat more satisfactory for routine use in these cases.

The diffuse hepatitis of late syphilis is to be classified clinically as a subacute or chronic process, by contrast with the acute process seen in the acute hepatitis of secondary syphilis or in postarsphenamine jaundice. The condition in the majority of these cases is apparently remediable, and the patients recover more or less completely under antisyphilitic treatment. This is not always so, however, for with sufficient injury there is permanent injury to the liver. Biliary cirrhosis results, and this must be looked on as the end-stage of the response of the liver to chronic injury. The possibility of the development of such a cirrhosis emphasizes the importance of prolonged observation of these patients, even after apparent clinical cure, before a decision is reached regarding the extent of residual injury to the liver.

35. Stokes, J. H.; Ruedemann, Rudolph, Jr., and Lemon, W. S.: Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:251 (Nov.) 1920.

Correspondence between the cases of portal cirrhosis in syphilitic and in nonsyphilitic patients also is to be noted. The clinical features and the symptoms, so far as the liver is concerned, are identical in the two groups. The changes in the various tests are alike, and the pathologic picture has no distinguishing features. It is difficult at times, even with the aid of microscopic studies, to determine what part syphilis alone has had in the development of this type of cirrhosis. On the other hand, it generally is accepted that portal cirrhosis represents the end-stage in the response of the liver to injury and represents the combined effect of the processes of degeneration, deposition of fibrous tissue and regeneration. An increasing number of cases has been collected and reported in which such cirrhosis has followed recovery from acute yellow atrophy. As syphilis is capable of producing acute destructive hepatitis of the type of acute yellow atrophy it is logical to assume that some of these cases of idiopathic portal cirrhosis were syphilitic in origin. Arsenic may produce a similar disturbance, whether given in inorganic form or as arsphenamine. Case 136 apparently is an example of such portal cirrhosis in a nonsyphilitic patient, which emphasizes the need for extreme care in the administration of arsphenamine in the presence of hepatic disease. The permanent and irremediable nature of the changes in the liver in portal cirrhosis emphasizes the importance of preventive rather than curative measures in treatment. In these cases, too, the bromsulphalein and phenoltetrachlorphthalein tests are of diagnostic and prognostic value as an index to the changes in the liver.

The picture of gumma of the liver is unusual in that the symptoms produced, as a rule, are much less distinct than ordinarily would be anticipated from the degree of hepatic involvement. The functional tests, especially the bromsulphalein or phenoltetrachlorphthalein tests, likewise show only minimal changes in the process of outspoken pathologic changes. The condition in gumma emphasizes the limitation in value of the different tests as affected by the type of lesion present. A diffuse lesion affecting the organ as a whole produces changes which are demonstrated readily. A localized lesion, such as a gumma, on the other hand, is limited in extent and the remainder of the organ may be relatively normal. In view of the large reserve in the liver, normal reactions are to be expected.

## SUMMARY

We are impressed with the varied types of hepatic disease that may be produced by a syphilitic infection, a condition that calls to mind the multiform lesions in the skin produced by the same infection. Consequently, it is necessary to speak not of syphilis of the liver in the general sense but rather of a specific type of hepatic lesion. The chief characteristics of the clinical pictures and the results of laboratory examina-

tions in these different conditions have been discussed. This discussion has emphasized the difficulty of differential diagnosis that frequently is encountered and the importance in making the diagnosis of using all available information, whether from history, general examination, laboratory tests, therapeutic trial or prolonged observation. The indications for the use of the different tests for hepatic function and their limitations have been discussed. These tests give results that are dependent on the extent and nature of the injury to the liver rather than on the specific etiologic agent concerned. For this reason, the probable type and extent of the pathologic process must be considered in interpreting the results of laboratory examination. When due regard is paid to these matters, the various tests of hepatic function have definite value in supplementing other methods of studying the patient.

# OPIUM ADDICTION

## VII. A COMPREHENSIVE STUDY OF EFFECTS OF THE SCOPOLAMINE TREATMENT FOR MORPHINE ADDICTION *

ARTHUR B. LIGHT, M.D.
AND
EDWARD G. TORRANCE, M.D.
PHILADELPHIA

The routine treatment that we have employed in the Philadelphia General Hospital has been confined chiefly to the scopolamine method. We have made studies of the addicts before treatment was begun and at intervals of from two to four days following the apparent cessation of the withdrawal symptoms, which were universally present while the patients were under the influence of scopolamine. During the latter study period, we encountered all grades of behavior and appearances of illness. We wish to report in this paper comparative studies made while morphine was being administered to supply the needs of the addict and again following the cessation of mental confusion produced by scopolamine. These studies include those of the heart and circulation, physical and chemical properties of the blood, metabolism, temperature, changes in weight, vital capacities, the urine, functional tests of the kidney and liver, and reaction to epinephrine and to atropine.

### METHOD OF TREATMENT

The routine method of treatment, which was carried out in a more or less uniform manner, is as follows: During the first twenty-four hours following admission, the patient is given morphine sulphate hypodermically in sufficient quantities to prevent withdrawal symptoms. If no studies during the administration of morphine are contemplated, he is placed on a liquid diet for this period. At the same time he is given a drastic dose of mild mercurous chloride or mass of mercury, U.S.P., followed in eight hours by a saline cathartic. At the end of the twenty-four hour period, scopolamine hydrobromide is given in doses of $\frac{1}{200}$ grain (0.3 mg.) hypodermically at four hour intervals, for three doses. With each dose of scopolamine is given $\frac{1}{40}$ grain (1 mg.) of strychnine

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* From the Narcotic Wards of the Philadelphia General Hospital.
* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and the work was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the Narcotic Wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

sulphate. Following this, the dosage of scopolamine is raised to $\frac{1}{150}$ grain (0.4 mg.) for three doses and then increased to $\frac{1}{100}$ grain (0.6 mg.) accompanied each time with $\frac{1}{40}$ grain strychnine. The total period covered by the administration of scopolamine covers thirty-six hours. When the effects of the scopolamine begin to disappear, if withdrawal symptoms are still quite severe, they are combated with large doses of phenobarbital, or frequently a single dose of $\frac{1}{4}$ grain (16 mg.) of morphine sulphate is given. Treatment from this time on is purely symptomatic, consisting chiefly of sedatives to promote sleep for three or four days as well as small doses of bicarbonate of soda for any gastric distress. Patients are usually discharged at the end of a period of ten days.

## EXPERIMENTAL PROCEDURE

These studies were usually conducted between the first and the fourth day following the disappearance of the mental confusion caused by the scopolamine. Practically all of our observations and studies were made during the morning hours while the subject was reclining in bed, not having had breakfast. The subjects were requested to recline in bed for a period of one-half hour. The figures for the pulse and respiration rates are the averages of a five minute count, and the figures for the blood pressure the average for as many determinations of pressure as could accurately be made in a five minute period. Following these observations, the basal metabolic rate and temperature were measured and recorded. Krogh's apparatus for recording the basal metabolism was used and checked once a week with a subject whose basal metabolic rate was known to be normal. Schneider's test for physical fitness [1] and determinations of vital capacity were usually next in order, followed by the taking of a sample of blood for analysis. The addict was then requested to pass a sample of urine, and following this he was subjected to the climb of two flights of stairs, as described by us in a previous paper.[2] Studies of the reaction to epinephrine and functional tests were carried out, as a rule, with the subjects reclining in bed. The procedure followed in the study of the effect of atropine sulphate on the P-R interval was the same as that described in the paper giving the results obtained during addiction.[2]

## RESULTS

Our results, shown in table 1, indicate that following treatment there was no change in the average pulse rate while the subjects were reclining

1. Schneider, Edward C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

2. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: III. The Circulation and Respiration of Human Addicts During the Administration of Morphine, Arch. Int. Med. **43**:556 (April) 1929.

and the average blood pressures while they were reclining and standing, but there was an average increase of 20 beats per minute in the pulse rate while the subjects were standing and an average increase of 3 respirations per minute while they were reclining. Fifteen of the twenty-three cases after treatment showed a rise in the pulse rate while the subjects were standing as compared to the average rate before treatment; in one, the rate remained the same and in four there was a slight decrease.

TABLE 1.—*A Comparison of the Circulation and Respiration of Human Opium Addicts Before and After Treatment with Scopolamine*

| | Before Treatment | After Treatment |
|---|---|---|
| Pulse Rate while Subject Was Reclining: | | |
| Number of cases | 50 | 23 |
| Highest | 84 | 96 |
| Lowest | 52 | 50 |
| Average | 65 | 68.5 |
| Pulse Rate while Subject Was Standing: | | |
| Number of cases | 30 | 23 |
| Highest | 112 | 134 |
| Lowest | 66 | 76 |
| Average | 79 | 99 |
| Blood Pressure while Subject Was Reclining: | | |
| Number of cases | 40 | 24 |
| Highest | 138/92 | 128/84 |
| Lowest | 98/62 | 102/64 |
| Average | 117/72 | 117/74 |
| Blood Pressure while Subject Was Standing: | | |
| Number of cases | 28 | 21 |
| Highest | 138/89 | 118/100 |
| Lowest | 88/64 | 90/ 60 |
| Average | 108/74 | 109/ 75 |
| Respirations: | | |
| Number of cases | 43 | 20 |
| Highest | 22 | 30 |
| Lowest | 10 | 13 |
| Average | 18 | 21 |

Measurements of the heart made by means of the orthodiagram in nine cases before and after treatment showed an average decrease in the ratio of the transverse diameter of the heart to that of the chest of from 44.4 to 41.2 per cent. The average diameter of the aortic arch remained the same, being 4.8 mm. after treatment and 4.7 mm. when morphine was being administered.

Table 2 contains a summary of the average changes obtained in the blood pressure and the pulse and respiration rates following the staircase climbing test both before and after treatment. Charts 1 and 2 show graphically the average absolute readings obtained. The response to staircase climbing following treatment compared with the results obtained during the administration of morphine shows that the immediate increase in the pulse rate was somewhat less than during the administration of the drug. The increase in the respiratory rate and

failure of the rise in systolic pressure to the height reached during the administration of morphine indicate a slightly poorer response following treatment, if the curves obtained from a series of trained athletes undergoing similar tests are used to show the response of an adequate circulation.

Electrocardiographic studies in a series of eight addicts before and after treatment showed no abnormal changes in the conformation of the various waves. There was a slight decrease in the average P-R interval following treatment, namely, from 0.15 to 0.145 second. At the same time, however, the average rate increased following treatment to 85 beats per minute as compared to 75.8 beats during the administration of morphine. The effect of the injection of $\frac{1}{20}$ grain (3 mg.) of atropine sulphate was no different after treatment from that while morphine was

TABLE 2.—*A Comparison of the Average Increases of the Pulse, Systolic Pressure and Respiration Rate and Changes in the Diastolic Pressure in Opium Addicts During Administration of Morphine and After Treatment with Scopolamine*

| | | Before Treatment | | | | | | After Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of Cases | 1st Reading | 1st Min. | 2d Min. | 3d Min. | 4th Min. | 5th Min. | 1st Reading | 1st Min. | 2d Min. | 3d Min. | 4th Min. | 5th Min. |
| Pulse | 9 | 62 | 37 | 20 | 13 | 11 | 12 | 57 | 34 | 15 | 6 | 4 | 4 |
| Systolic pressure | 9 | 29 | 30 | 25 | 16 | 9 | 4 | 19 | 23 | 19 | 13 | 7 | 3 |
| Diastolic pressure | 9 | −10 | −7 | −6 | −6 | −6 | −6 | −12 | −7 | −5 | −4 | −1 | −0 |
| Respirations | 9 | .. | 5 | 2 | 1 | 1 | 1 | .. | 9 | 5 | 3 | 2 | 1 |

still being administered. In both studies the P-R interval was decreased 0.02 second, the average decrease coming at approximately the same time, namely, 14.5 minutes before and 12 minutes following treatment. The effect of the atropine on the heart rate was unchanged by treatment. In both instances, the percentage of increase of the heart rate was 45, and the average time of the greatest increase 24.7 minutes during the administration of morphine and 22 minutes following the treatment.

Schneider's test of physical fitness showed a decided fall in the average number of points scored following treatment. Seventeen cases studied during the administration of morphine scored an average of 13.3 points, while the average score following treatment was only 6.9 points. Fifteen of the seventeen cases showed this fall in score, one case scoring the same number of points; the two remaining cases showed a rise of two points following treatment.

Vital capacities in eight cases averaged practically the same while the subjects were receiving morphine as compared to the average obtained following the administration of scopolamine, namely, 4,047 cc. before treatment and 4,016 cc. following treatment.

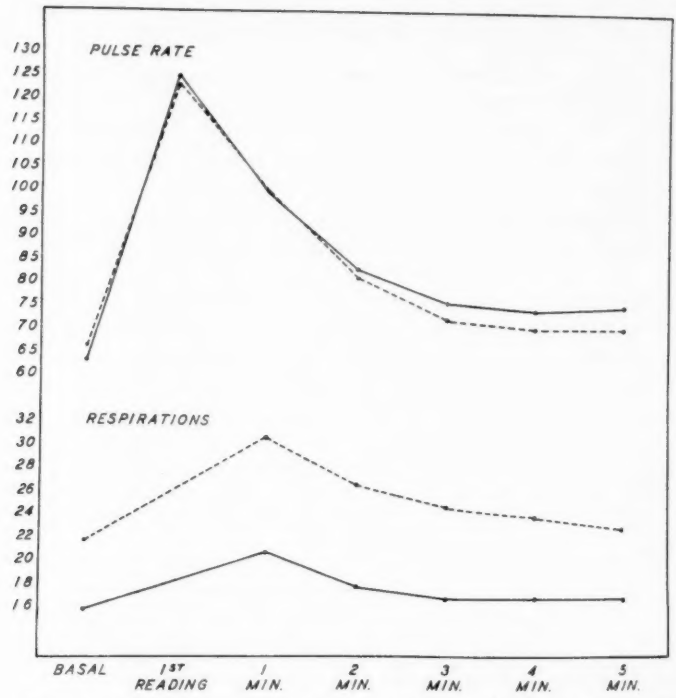


Chart 1.—Average changes in the pulse and respiration rates, in response to staircase climbing test in a group of human addicts receiving morphine and following treatment with scopolamine. In this chart and in charts 2 and 3, the solid line indicates before treatment and the broken line, after treatment.

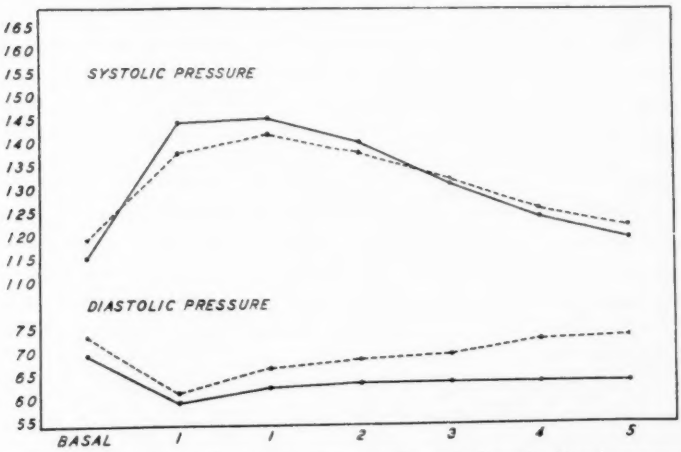


Chart 2.—Average changes in the systolic and diastolic blood pressure in response to the staircase climbing test in a group of human addicts receiving morphine and following treatment with scopolamine.

*The Blood.*—Results obtained from studies of the blood before and after treatment, given in table 3, show practically no significant changes. The average number of red blood cells has increased slightly, namely, 177,000 per cubic millimeter when compared to the results obtained

TABLE 3.—*A Comparison of the Physical and Chemical Properties of the Blood of Human Opium Addicts Before and After Treatment with Scopolamine*

| | Hemoglobin, Gm. per 100 Cc. | | Erythrocytes, Number per C Mm. | | Leukocytes, Number per C.Mm. | | Polymorphonuclears, per Cent | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 26 | 19 | 29 | 10 | 33 | 10 | 28 | 7 |
| Highest..... | 19.4 | 18.4 | 4,980 | 5,100 | 15,400 | 16,400 | 78 | 80 |
| Lowest..... | 12.0 | 13.2 | 3,640 | 4,395 | 2,500 | 4,000 | 33 | 45 |
| Average..... | 15.2 | 15.8 | 4,533 | 4,710 | 9,359 | 11,166 | 61 | 61 |

| | Lymphocytes, per Cent | | Large Mononuclears, per Cent | | Eosinophils, per Cent | | Basophils, per Cent | | Blood Urea Nitrogen, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 28 | 7 | 28 | 7 | 28 | 7 | 28 | 7 | 28 | 16 |
| Highest..... | 63 | 53 | 7 | 7 | 2 | 2 | 3 | 2 | 24 | 20 |
| Lowest..... | 20 | 19 | 0 | ½ | 0 | 0 | 0 | 0 | 10 | 9 |
| Average..... | 34 | 35 | 3 | 3 | ½ | ½ | 1½ | ½ | 13.2 | 14 |

| | Blood Sugar, Mg. per 100 Cc. | | Blood Uric Acid, Mg. per 100 Cc. | | Blood Lactic Acid, Mg. per 100 Cc. | | Blood Cholesterol, Mg. per 100 Cc. | | Blood Sodium Chloride, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 32 | 16 | 22 | 12 | 6 | 6 | 16 | 18 | 9 | 2 |
| Highest..... | 122 | 166 | 4.5 | 4.8 | 31.1 | 38.4 | 280 | 274 | 570 | 560 |
| Lowest..... | 72 | 80 | 2.4 | 2.4 | 20.1 | 22.6 | 158 | 120 | 480 | 490 |
| Average..... | 97 | 100 | 3.3 | 3.4 | 25.0 | 31.8 | 208 | 198 | 511 | 525 |

| | Serum Calcium, Mg. per 100 Cc. | | Serum Phosphate, Mg. of Phosphorus per 100 Cc. | | *pH* Plasma | | Carbon Dioxide Capacity of Plasma, per Cent by Volume | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 14 | 5 | 11 | 5 | 20 | 10 | 20 | 10 |
| Highest..... | 14.4 | 13.1 | 3.2 | 2.8 | 7.51 | 7.45 | 71 | 63 |
| Lowest..... | 9.8 | 10.1 | 2.6 | 2.2 | 7.28 | 7.33 | 45 | 48 |
| Average..... | 10.9 | 11.7 | 2.8 | 2.6 | 7.36 | 7.41 | 57.7 | 52 |

| | Dry Matter of Whole Blood, per Cent | | Dry Matter of Plasma, per Cent | | Dry Matter of Cells, per Cent | | Red Blood Cells, per Cent by Volume | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 22 | 17 | 15 | 11 | 7 | 8 | 6 | 10 |
| Highest..... | 22.7 | 23.6 | 10.2 | 10.4 | 48.0 | 41.8 | 38.7 | 49.0 |
| Lowest..... | 15.7 | 18.0 | 5.3 | 6.8 | 38.2 | 38.3 | 34.0 | 36.0 |
| Average..... | 20.1 | 21.49 | 8.4 | 9.01 | 41.2 | 40.2 | 36.2 | 39.4 |

before treatment. The number of white cells has also increased from an average of 9,359 to 11,166. Hemoglobin, differential counts of the white cells and determinations of urea nitrogen, sugar, uric acid, cholesterol, whole blood chloride, serum calcium and serum phosphate all show average results similar to those obtained during addiction. Dry matter of the plasma and of the whole blood has increased slightly, with a slight fall

in the dry matter of the cells. The average $p_H$ of the blood has risen from 7.36 to 7.41 following treatment, the carbon dioxide capacity of the plasma having fallen from 57.7 to 52 per cent by volume. The average per cent by volume of the red blood cells has increased slightly from 36.2 to 39.4, while the lactic acid of the blood also shows a slight increase following treatment from an average of 25 to 31 mg. per hundred cubic centimeters of blood.

Sedimentation tests in twelve cases before and after treatment showed parallel curves indicating no change. Studies of the viscosity of the blood in five cases showed no difference before and after treatment.

*Metabolism.*—The basal metabolic rates of ten addicts obtained during the administration of morphine and again after treatment remained strikingly constant. The average range before treatment was between —9 and +9 and following treatment between —14 and +9. Individual determinations showed the lowest and highest rates before treatment to be —26 and +28 and following treatment —28 and +26.

*Changes in Weight.*—The loss of weight during treatment in some cases was striking. Twenty patients whose weights were taken just before and after treatment showed an average loss of 7 pounds (3.2 Kg.). The greatest loss was 18 pounds (8.2 Kg.), while one patient actually gained 3 pounds (1.4 Kg.). The other eighteen cases showed losses of weight of from 2 to 12 pounds (0.9 to 5.4 Kg.), respectively.

*Temperature.*—Temperatures taken in a series of 100 addicts during treatment and for a period of three days following the cessation of the administration of scopolamine showed a slight rise for forty-eight hours in seventy-eight of the cases. The highest temperature recorded was 100.8 F., the average maximum temperature in the seventy-eight cases being 99.4. These patients were all free from abscesses and intercurrent infections. This slight rise in temperature rarely continued for more than forty-eight hours, although one addict had an average temperature of 99.2 for a period of five days, which rose at times to as high as 100.

*The Kidneys.*—The urines of 100 addicts showed a definite rise in the average specific gravity of from 1.018 to 1.026, with a distinctly lower twenty-four hour output following treatment. In two cases, a trace of sugar was found with Benedict's test following treatment. Thirty-two cases showed the presence of from a trace to a light cloud of albumin, ten cases showing a few granular and hyaline casts. Spermatozoa were frequently found in the urine following treatment.

Phenolsulphonphthalein tests in eight cases studied before and after treatment showed an average two hour elimination of 64 per cent of the dye before treatment and of 48 per cent after treatment. Five of these eight cases showed albumin in the urine following treatment, one

case showing a light cloud. The latter patient eliminated 49 per cent of the dye before treatment and only 16 per cent following treatment during the two hour periods. The other seven cases showed slight decreases in the amounts excreted after treatment compared to the results obtained during the administration of morphine.

*The Liver.*—The phenoltetrachlorphthalein test carried out in four cases showed no delay in the disappearance of the dye in two hours either before or after treatment. Van den Bergh's tests remained negative in four cases both before and after treatment. An average icterus index of 6.1 was obtained following treatment as compared to an average of 5.5 obtained before treatment.

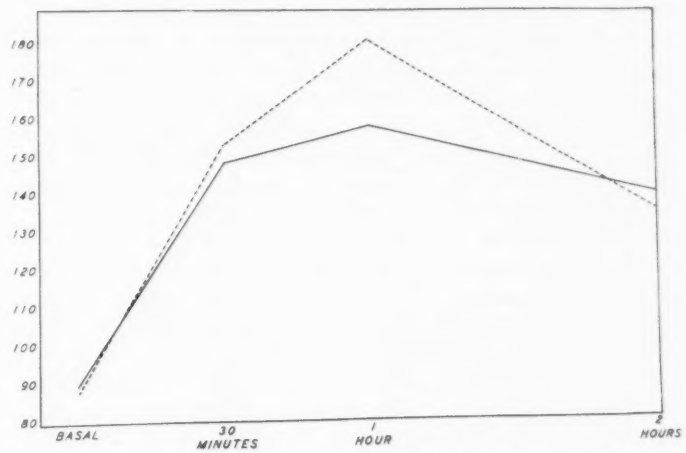


Chart 3.—Average blood sugar response to the injection of 1 cc. of epinephrine hydrochloride (1 : 1,000) in a group of human addicts receiving morphine, and after treatment with scopolamine.

*Blood Sugar Response to Epinephrine.*—Chart 3 shows graphically the blood sugar response in a series of five addicts who were given 1 cc. of 1 : 1,000 epinephrine hydrochloride both before and after treatment. The curves show that the blood sugar content rises slightly higher following treatment as compared to the rise while morphine is being administered. Determinations of blood pressure were also made, but the results were so variable as to make any comparison doubtful in value.

## COMMENT AND LITERATURE

The interpretation of our results in the light of the behavior and appearance of the addicts following treatment is extremely difficult.

The effect of the drastic purgation and the scopolamine itself must be considered in the production of the changes observed, but in general

our observations following treatment are more or less similar to those obtained during a series of studies made following a forty-eight hour period of abrupt withdrawal without the substitution of any other drug.[3]

Lambert and Tilney [4] studied the blood of a series of opium addicts before and during treatment with narcosan. They did not find any changes in the uric acid and creatinine of the blood either before or during treatment. Wide fluctuations of the blood sugar, which we interpret as being standard, are reported one hour after breakfast was taken. Our blood sugar values remained constant in specimens taken before and after treatment while the addict was fasting. Lambert and Tilney [4] also found considerable fluctuation of the carbon dioxide chemically bound in the plasma and detected an increase in acidosis for the first three days of treatment. In the majority of our cases, the average $p_H$ of the blood shows a tendency for a slight increase in the alkalinity following treatment. Our blood cell determinations are similar to those obtained by Lambert and Tilney except that we encountered certain slight degrees of leukocytosis before treatment was begun. Our urinary observations are also identical with those of Lambert and Tilney.[4]

In a comparative study of the efficiency of the narcosan treatment with the routine treatment employed in the Colorado Psychopathic Hospital, Johnson [5] was unable to detect any significant changes in the blood. He found but one abnormal blood sugar value, while his figures for blood urea nitrogen were well within normal limits. Johnson found a leukocytosis in most cases during narcosan treatment, the actual figures obtained ranging between 5,400 and 19,300 cells.

Immediately following treatment, the appearance and behavior of the addicts are misleading. It has been our frequent experience to have two addicts in the ward whose needs were supplied with the same amount of morphine and who were given identical treatment at the same time. At the end of the fourth day, one addict will be up and about the ward with the declaration that he feels fine and will eat well and boastfully proclaim that he is through with the drug. The other addict will remain in bed, refuse food, appear miserable and complain bitterly of extreme weakness and nervousness. We believe that frequently neither of these two types is expressing or acting his real self. The addict who proclaims his well-being may or may not show the few posi-

3. Light, Arthur B., and Torrance, Edward G.: Opium Addiction. VI. The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts with Special Reference to the Composition of the Blood, the Circulation and the Metabolism, Arch. Int. Med. **44**:1 (July) 1929.

4. Lambert, Alexander, and Tilney, Frederick: Treatment of Narcotic Addiction by Narcosan, M. J. & Rec. **124**:764 (Dec. 15) 1926.

5. Johnson, George S.: The Use of Narcosan in the Treatment of Drug Addiction, Colorado Med. **24**:347 (Nov.) 1927.

tive changes we have previously noted. We are convinced that a good deal of this behavior is feigned, and that the addict is trying to gain his discharge in order that he may return to his friends who will again supply him with drugs.

The other addict who complains of being so miserable and weak and nervous may or may not show any of the positive symptoms previously mentioned. This behavior is frequently found in addicts who are penniless and who do not know where to turn for drugs when discharged from the ward.

It is during this period of the addict's stay in the ward that our method of treatment is characterized as being the best or the worst that the addict has ever undergone.

Few of our addicts have not had treatments before. Many of them have tried every method employed for the treatment of narcotic addiction. Their comments as to the efficacy of these various forms of treatment are totally unreliable. It is our opinion, however, from the number of addicts who have come to us from other institutions and the fact that 50 per cent come back to us for another treatment, that present methods, including our own, leave much to be desired.

## CONCLUSIONS

Studies of a series of opium addicts before and after treatment with scopolamine revealed the following positive changes: loss of weight, slight rise in temperature, appearance of albuminuria, slight leukocytosis, slight concentration of the blood, a rise in the $p_H$ of the blood, a rise in the lactic acid of the blood, a fall in the carbon dioxide capacity and a fall in the total number of points scored with Schneider's test of physical fitness.

No significant changes were found in a comparison of the pulse, respiration rates and blood pressure while the addict was reclining, heart measurements, electrocardiographic studies, staircase climbing tests, effect of atropine sulphate on the P-R interval, vital capacities, blood urea nitrogen, blood sugar, blood uric acid, blood cholesterol, whole blood chloride, serum calcium and phosphate, blood viscosity, sedimentation tests, basal metabolism, phenolsulphonphthalein tests, phenoltetrachlorphthalein test of liver function, icterus index, van den Bergh's tests, and response of the blood sugar to epinephrine.

The few positive observations do not coincide with the general appearance and behavior of the addict. He may present some or all of the foregoing positive symptoms and yet appear and behave as though he were normal. On the other hand, he may give the appearance of one who is quite ill and yet not show any of the foregoing positive symptoms.

# BLUEBERRY LEAF EXTRACT OVERDOSAGE *

LEONARD BENJAMIN SHPINER, B.S.
CHICAGO

In a recent paper [1] I corroborated the work of Allen [2] on blueberry leaf extract, now called "myrtomel," and extended it further by investigating its effect on thyroid hyperglycemia and glycosuria. Because of the possible demand for blueberry leaf extract in treating patients with mild diabetes, it seemed imperative at this time to study the effect of overdosage with blueberry leaf extract, particularly since von Noorden [3] published data purporting to show that this drug causes focal necrosis in the liver following intravenous injection. It seemed to me that this method of biologic assay is unwarranted, since the preparation of the drug available at the present time is too crude for parenteral, least of all intravenous, injection. Because of these considerations, it seemed important to determine whether the oral administration of the drug in dosages even greater than those prescribed for man exerted any detectable deleterious effect.

## METHODS

Four dogs were put on a daily standard diet of 250 Gm. of beef heart, 100 Gm. of bread and 250 cc. of milk. This diet, sufficient for their caloric needs, was not changed during the course of the experiment. The total output of urine was recorded and samples were taken for daily analysis. Toluene was used as a preservative to minimize bacterial decomposition. At the time the samples of urine were taken, from 5 to 6 cc. of blood was withdrawn from the saphenous vein and put in tubes containing powdered potassium oxalate as an anticoagulant.

To test qualitatively for urinary sugar, Fehling's or Benedict's reagents were used. If the tests were negative, the samples were discarded; if positive, the amount of blood and urinary sugar was determined by the method of Folin-Wu, two determinations being made on each sample.

The Folin-Wu method was used to determine the amount of blood sugar. Two blood sugar determinations were made daily, the average being recorded as the blood sugar level for that day.

Control experiments were made on the animals three or more days before preparing them for initial experiments.

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* From the Hull Physiological Laboratory, University of Chicago.

* Aided by a grant from the Frank Billings Medical Research Club, Chicago.

1. Shpiner, L. B.: Am. J. Physiol. **84**:396, 1928.

2. Allen, F. M.: Blueberry Leaf Extract: Physiologic and Clinical Properties in Relation to Carbohydrate Metabolism, J. A. M. A. **89**:1577 (Nov. 5) 1927.

3. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, Berlin, A. Hirschwald, 1927. Blueberry Leaf Extract: Preliminary Report of Council on Pharmacy and Chemistry, J. A. M. A. **89**:1607 (Nov. 5) 1927.

The effect of overdosage with blueberry leaf extract was studied on two normal and two partially pancreatectomized dogs. After a control period of three or more days, the dogs were operated on. Pieces of liver and pancreas were removed for microscopic examination. In performing a partial pancreatectomy, nineteen twentieths of the pancreas was removed, the remnant being connected to the duodenum through the duct of Santorini. At the conclusion of the experiment, a biopsy was again performed. The removed hepatic and pancreatic tissue was fixed, stained and compared with the sections of the liver and pancreas taken from the animal when it was in a normal state.

In studying the effects of blueberry leaf extract,[4] from six to twelve tablets (5 grains [0.324 Gm.] per tablet) were given at least one hour before feeding time. This dosage represents from two to four times the dosage of blueberry leaf extract necessary for its therapeutic effect in man.

Sections of the pancreas were fixed with Bensley's[5] A.O.B. and stained for study of islet tissue, and also with hematoxylin and eosin. Sections of the liver were stained with Best's[6] carmine method for glycogen.

Phenolsulphonphthalein was used in studying renal function. The drug was administered intravenously, and collections of urine for a study of the rate of elimination of the dye were limited to one hour.

(*a*) Normal dogs were fed a control diet for twelve days. The low blood sugar content was 80 mg. per hundred cubic centimeters; the high content was 90 mg. The urine did not contain sugar. The average volume of urine was 250 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 76.6 per cent.

(*b* and *c*) A piece of liver and pancreas was removed for microscopic examination. In the postoperative period (seven days) the dogs were maintained on a high fluid diet plus six tablets of blueberry leaf extract. The low blood sugar content was 84 mg. per hundred cubic centimeters; the high content was 91 mg. The urine did not contain sugar. The average volume of urine was 202 cc. The average excretion of phenolsulphonphthalein in the first hour was 80 per cent.

(*d*) A control diet plus six tablets of blueberry leaf extract were given for eight days. The low blood sugar content was 85 mg. per hundred cubic centimeters; the high content was 92 mg. The urine did not contain sugar. The average volume of urine was 316 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 76.7 per cent.

(*e*) A control diet plus twelve tablets of blueberry leaf extract were given for fifteen days. The low blood sugar content was 81 mg. per

4. The blueberry leaf extract used in these experiments was furnished by E. R. Squibb & Sons, New Brunswick, N. J.

5. Bensley, R. R.: Harvey Lectures, 1914-1915, p. 250. The formula for Bensley's A.O.B. fixing fluid is: glacial acetic acid, 1 drop; 2 parts of 2 per cent aqueous solution of osmic acid, and 8 parts of 3 per cent potassium bichromate.

6. Best: Pathological Technique, ed. 8, Philadelphia, Mallory & Wright, 1924, p. 199.

hundred cubic centimeters; the high content was 89 mg. The urine did not contain sugar. The average volume of urine was 280 cc. The average secretion of phenolsulphonphthalein in the first hour was 78.7 per cent.

(*f*) A control diet plus six tablets of blueberry leaf extract were given for eight days. The low blood sugar content was 82 mg. per hundred cubic centimeters; the high content was 85 mg. The urine did not contain sugar. The average volume of urine was 280 cc. The average excretion of phenolsulphonphthalein in the first hour was 76.6 per cent.

(*g*) A control diet and blueberry leaf extract were given for eight days. At the end of this time, the low blood sugar content was 84 mg. per hundred cubic centimeters; the high content was 90 mg. The urine did not contain sugar. The average volume of urine was 316 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 78.3 per cent.

(*h*) A control diet plus twelve tablets of blueberry leaf extract were given for forty-three days. The low blood sugar content was 83 mg. per hundred cubic centimeters; the high content was 98 mg. The urine did not contain sugar. The average volume of urine was 316 cc. The average excretion of phenolsulphonphthalein in the first hour was 77 per cent.

At the end of the experiment, a piece of liver and one of pancreas were fixed, stained and examined microscopically.

As can be seen from the results given, blueberry leaf extract in from two to four times the therapeutic dose has no effect on normal dogs. The blood sugar remains normal and there is a slight polyuria, but the rate of the excretion of phenolsulphonphthalein remains within normal limits. During the experimental period, the temperature, pulse, respiration and body weight do not vary from the normal. Microscopic examination of the pancreas fixed and stained with the A.O.B. method and hematoxylin and eosin shows no increase in the islet or acinar tissue. Sections of the pancreas resemble normal pancreas taken during the control period.

Best's carmine method for glycogen reveals neither an increase nor a decrease in glycogen content of the liver cells.

The results obtained on the partially pancreatectomized dogs (nineteen-twentieths) were as follows:

(*a*) A dog was fed a control diet for six days, The low blood sugar content was 80 mg. per hundred cubic centimeters; the high content was 86 mg. The urine did not contain sugar. The average volume of urine was 317 cc. The average excretion of phenolsulphonphthalein in the first hour was 78.3 per cent.

(*b* and *c*) A subtotal pancreatectomy was performed (nineteen-twentieths of the gland was removed). In the postoperative control period (*c*) the animal was given a fluid diet plus six tablets of blueberry leaf extract for five days. The low blood sugar content was 85 mg. per hundred cubic centimeters; the high content was 130 mg. The urine did not contain sugar. The average volume of urine was 216 cc. The average amount of phenolsulphonphthalein excreted was 80 per cent.

(*d*) An animal was fed a control diet plus six tablets of blueberry leaf extract for ten days. The low blood sugar content was 98 mg. per hundred cubic centimeters; the high content was 130 mg. The urine did not contain sugar. The average volume of urine was 351 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 80 per cent.

(*e*) An animal was fed a control diet plus twelve tablets of blueberry leaf extract for seventeen days. The low blood sugar content was 91 mg. per hundred cubic centimeters; the high content was 97 mg. The urine did not contain sugar. The average volume of urine was 335 cc. The average excretion of phenolsulphonphthalein in the first hour was 79 per cent.

(*f*) A control diet plus six tablets of blueberry leaf extract were given the animals for seven days. The low blood sugar content was 82 mg. per hundred cubic centimeters with a high content of 89 mg. The urine did not contain sugar. The average volume of urine was 426 cc. The average excretion of phenolsulphonphthalein in the first hour was 77.5 per cent.

(*g*) A control diet of twelve tablets of blueberry leaf extract was given for eighteen days. The low blood sugar content was 88 mg. per hundred cubic centimeters; the high content was 102 mg. The urine did not contain sugar. The average volume of urine was 439 cc. The average excretion of phenolsulphonphthalein in the first hour was 77 per cent.

(*h*) A control diet without blueberry leaf extract was given to the dogs for seven days. The low blood sugar content was 90 mg. per hundred cubic centimeters, with a high content of 98 mg. The urine did not contain sugar. The average volume of urine was 417 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 77.5 per cent.

(*i*) A control diet plue twelve tablets of blueberry leaf extract were given for fourteen days. The low blood sugar content was 86 mg. per hundred cubic centimeters; the high content was 98 mg. The urine did not contain sugar. The average volume of urine was 408 cc. The average excretion of phenolsulphonphthalein in the first hour was 78 per cent.

At the end of the experiment a piece of pancreas and a piece of liver were removed, fixed, stained and examined microscopically.

Removal of nineteen-twentieths of the pancreas leads to diabetes; in the dogs kept on doses of blueberry leaf extract, however, diabetes did not develop. The experiment corroborated results obtained by Allen on similar dogs. In only one of the dogs did hyperglycemia develop after removal of the blueberry leaf extract from the diet. But on subsequent feeding of blueberry leaf extract followed by its removal from the diet, a hyperglycemia and glycosuria did not again develop. During the experimental period, the temperature, pulse, respiration and body weight did not vary from those of the normal period.

Here, as well as in normal dogs, no derangement of kidney function was noted. The hyperglycemia and glycosuria were controlled by the feeding of blueberry leaf extract, and the excretion of phenolsulphonphthalein dye remained within normal limits.

Microscopic sections of pancreas, as examined by Bensley's A.O.B. method and hematoxylin and eosin, showed regeneration of acinar, but not of islet tissue.

Sections of the liver examined by Best's carmine stain showed about the same amount of glycogen as in the sections of normal liver. This indicates that there was no depletion in the amount of glycogen in the liver following the period of partial pancreatectomy plus the feeding of blueberry leaf extract. Furthermore, there was no indication of focal necrosis.

## COMMENT

The results in my experiments indicate that overdosage with blueberry leaf extract (myrtomel), both in normal and in partially pancreatectomized dogs, is without detectable effect. Assuming that the average weight of a dog is one-fifth that of man, I have fed dogs, on the basis of body weight, twenty times the therapeutic dose over a period representing 4.9 per cent of the life span of man without any noticeable untoward systemic effects.

## CONCLUSIONS

On the basis of my experiments I conclude that:

Blueberry leaf extract is nontoxic to normal and partially pancreatectomized dogs when administered orally in what may be considered excessive doses.

Its clinical trial in diabetes, therefore, is not fraught with any undesirable effects or possibilities.

# THE RETICULOCYTE COUNT IN NORMAL AND IN ABNORMAL CONDITIONS*

ALFRED FRIEDLANDER, M.D.
AND
CHARLOTTE WIEDEMER, M.D.
CINCINNATI

Since the advent of vital staining, interest in the reticulocyte count as one index of regeneration of the blood has been much heightened.

Among the earlier investigators to study reticulation was Ehrlich,[1] who by means of a dried blood film stained with a saturated solution of methylene blue (methylthionine chloride, U. S. P.), described nets in the red corpuscles in normal blood and in anemia. Twelve years later Askanazy[2] noted a reticulated substance in the erythrocytes of a rapidly progressive anemia. In 1901, Levaditi[3] began the use of a brilliant cresyl blue as a vital stain, but did not mention reticulation. From 1907 to 1913 much work was done on reticulation. A brief summary of these studies will be found in Cunningham's article.[4] In his own work Cunningham[4] found that permanent preparations could be made by combining a vital stain with Wright's stain. He thought that the ease and simplicity of this method would bring the study of reticulated erythrocytes within the scope of routine blood examinations. In this method a small drop of 0.3 or 0.5 per cent solution of brilliant cresyl blue is placed on a clean slide or cover glass, smeared around over an area of 1.5 cm. and allowed to dry. A drop of blood on a cover-slip is then dropped face down on the area of dried stain. After drying, the film is stained with Wright's stain. This method is similar to that advocated by Hawes[5] in 1909.

Many authors use this method also for the counting of the reticulocytes. One thousand red cells are counted in fields of about fifty, the reticulated cells seen during the counting process being enumerated. This method is open to the criticisms that the dye or cells or both may not be evenly spread, that some of the reticulated cells may wander to the edges and that the dye might not penetrate a thick specimen.

For these reasons and for the purpose of securing the greatest possible accuracy in reticulate counts, we have adopted another method to be described presently.

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* From the Department of Internal Medicine, College of Medicine, University of Cincinnati.

1. Ehrlich, P.: Berl. klin. Wchnschr. **3**:43, 1881.
2. Askanazy, S.: Ztschr. f. klin. Med. **23**:80, 1893.
3. Levaditi, C.: J. de physiol. et de path. gén. **3**:425, 1901.
4. Cunningham, T. D.: Method for Permanent Staining of Reticulated Red Cells, Arch. Int. Med. **26**:405 (Oct.) 1920.
5. Hawes, J. B., Jr.: Boston M. & S. J. **161**:493, 1909.

Krumbhaar [6] drew the blood to be counted into a leukocyte counting pipet, using a dilute solution of brilliant cresyl blue as the diluent. After thorough shaking, a wet cover slip preparation is made from the content of the pipet, ringed with petrolatum and then counted in the usual manner, counting 1,000 cells.

Seyfarth [7] used a fresh preparation with a square cover glass and an ocular graduated for counting. He emphasized the fact that stained slides are not good for the counting of reticulocytes, as the methyl alcohol fixation causes some of the granules to disappear. He also thought that the centrifugation methods of Abrami and Brule are not applicable for reticulocyte counting. After centrifugation the granule-containing cells are not evenly distributed throughout the entire mass.

McCord,[8] desiring a quick and approximately quantitative method to be used chiefly among lead workers, used the following: He made a thick smear of blood and, without fixing, stained with a dilute solution of a modified Manson's methylene blue. With this stain, only the shadowy outlines of the normal erythrocytes are seen, while the reticulocytes and stippled cells show blue reticulation or granules within this outline. He then counted the number of such cells in ten oil immersion fields and took the average number per field. The objections to this method are that it is not accurately quantitative and that the stain is relatively unstable. We have found that a solution of polychrome methylene blue will give the same results, and that it is much more stable.

## METHOD

The method we have worked out has been described in a previous paper.[9] Because of its simplicity, and because of recent modifications, it is described in detail here.

A specific pipet for the making of a blood dilution of 1:20, instead of the usual white cell pipet (dilution 1:10), is used. A microscopic objective, giving a magnification higher than the ordinary 4 mm. lens, is of advantage. We have used a no. 7 Leitz or a DD Zeiss. The oil immersion lens cannot be used.

The solutions needed are:

1. A 1 per cent aqueous solution of brilliant cresyl blue. We have used the Gruebler, natural aniline and Coleman-Bell dyes. The Coleman-Bell dye has given the best results.
2. A diluent solution containing 0.6 Gm. of sodium chloride and 0.2 Gm. of potassium oxalate to 100 cc. of distilled water.

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6. Krumbhaar, E. B.: J. Lab. & Clin. Med. **8**:11, 1922-1923.
7. Seyfarth, C.: Folia haemat. **34**:7, 1927.
8. McCord, C. P.: The Basophilic Aggregation Test in Lead Poisoning, J. A. M. A. **82**:1759 (May 31) 1924; Bull. U. S. Bureau Labor Statistics, April, 1928, no. 460.
9. Friedlander, A., and Wiedemer, C.: Basophilic Aggregation in New-Born, Am. J. Dis. Child. **30**:804 (Dec.) 1925.

These are the stock solutions. They can be kept indefinitely in a cool place. As needed, another dilute solution is made up as follows:

Two cubic centimeters of the brilliant cresyl blue solution (solution 1) is added to 8 cc. of the diluent solution (solution 2), which makes a 0.2 per cent solution of brilliant cresyl blue. This solution (solution 3) must be made up fresh about once a week. It is necessary to vary the dilution from time to time, depending on the dye used.

The blood is drawn up to the 0.5 mark of the pipet with a dilution of 1:20, then it is diluted to the 21 mark with the 0.2 per cent brilliant cresyl blue solution (solution 3). The pipet is shaken thoroughly, allowed to stand for ten minutes or more and then shaken well again. The blood is then ready for counting. The ordinary counting chamber is used, and the squares are counted as they are in the ordinary white cell count. In calculating the result it must be remembered that the dilution is twice that of the ordinary white cell count. The blood, diluted in this way, may stand twenty-four hours without injury to the cells, but after this period the count is not accurate. To count the reticulocytes, it is necessary to have a good light, preferably artificial, and an especially high magnification dry lens as before mentioned. With this dilution of stain, the white blood cells stain dark blue. The red cells have a pale yellow cast, but show up blue. The reticulocytes are easily recognized by the blue reticulum or granules in their cytoplasm. The various forms of reticulocytes, as enumerated by Seyfarth,[7] are brought out distinctly. These vary from the earliest forms, with dense reticulum in the center of the cells so that they resemble normoblasts, to the more mature forms showing only a few scattered basophilic granules.

When normoblasts or megaloblasts are present, there is a distinct difference in staining reaction between the nuclear and reticular material. The nuclear material stains purple; the reticular substance stains blue.

This method overcomes the chief objections to the Cunningham method,[4] which is the method in general use. In the Cunningham method the stain does not come in contact with all cells of the blood droplet, and the reticulocytes are not evenly distributed over the slide. It is much simpler than counting 1,000 red cells in a stained preparation. As a matter of fact, by this method a reticulocyte count can be done as easily, and almost as quickly, as a white cell count after some experience has been had with the method.

## EXPERIMENTAL STUDIES

The figures as to the reticulocyte count in normal persons, as given in the literature, show great variations. It is even stated that the normal reticulocyte count runs to 1 or 1.5 per cent of the red cell count. On a basis of 5,000,000 red cells, this would mean an average of from 50,000 to 75,000 reticulocytes per cubic millimeter for the normal person. We are convinced that these figures are much too high. As a basis for our studies of the reticulocyte count in pathologic conditions, and as a test of our method, we made complete blood counts, including reticulocyte counts, on ninety-three persons, all in good health as far as we could ascertain. In addition to the complete count, the reticulocyte count was done, in each instance, by three methods, i. e., Cunningham's, McCord's and our own.

As our figures for the reticulocyte count, however, were lower than those usually given in the literature, the criticism of our method was made that the diluting stain hemolyzed the reticulocytes. This would give us lower counts. *A priori* we felt that this criticism was probably not justified because, as has been shown by Buckman and MacNaugher,[10] reticulocytes, except in pernicious anemia, are less fragile than mature erythrocytes. To meet this criticism, however, we made parallel counts on seventy-two of the normal persons studied. In one red cell count we used the Hayem's solution as ordinarily employed. In the other, we used, as the blood diluting fluid, the 0.2 per cent brilliant cresyl blue solution, as used for our reticulocyte counts. These red cell counts, as shown by our studies, vary only between experimental limits.

The reticulocyte count on normal persons is also compared in the accompanying tables, as done by the Cunningham, McCord and our method. One series of counts was made during the winter months; a second was made during the spring months. In forty-six normal persons studied during the winter months (from November 17 to March 10), the counts ran as follows: Cunningham, from 0 to 0.7 per cent, average 0.22 per cent; McCord, from 0 to 1.8 per cent, average 0.4 per cent; Friedlander and Wiedemer, from 0 to 0.1 per cent; average 0.03 per cent. In forty-seven normal persons studied during the spring months (from March 10 to May 30), the figures were as follows: Cunningham, from 0 to 1 per cent, average 0.3 per cent; McCord, from 0.2 to 1.7 per cent, average 0.78 per cent;; Friedlander and Wiedemer, from 0.03 to 0.4 per cent, average 0.18 per cent.

It will be noted that during the winter months, the counts on normal persons were seven times as high by the Cunningham method as by our method; during the spring months, they were twice as high. In each instance figures for the McCord method were twice as high as those for the Cunningham method.

We are convinced, as shown by our accurate quantitative counts, that the figures as ordinarily reported for the reticulocyte count in normal persons are much too high. We believe that the reticulocyte count in normal persons runs from about 0.03 to 0.2 per cent, that is, from 1,500 to 10,000 reticulocytes per cubic millimeter, depending on the time of the year. We are also inclined to the belief that by our method the reticulocyte counts on normal persons run much more consistently than by the Cunningham method, which gives a much greater variation than we obtain.

The foregoing counts were done on healthy adults of both sexes between the ages of 20 and 50. Most of them were physicians, nurses and medical students. The counts were begun in the winter and all

10. Buckman, T. E., and MacNaugher, E.: J. M. Research **44**:61, 1923.

ran low—from 1,000 to 2,000 reticulocytes per cubic millimeter. As the work continued into the spring months, the counts began to run higher, up to 20,000. Thinking that there might be a definite seasonal variation, we made rechecks of counts on persons on whom the counts had been made during the winter months. The results in sixteen of the persons studied are shown in table 1.

In each instance, comparative counts on the same person made during the winter and spring months are shown on the same line of table

TABLE 1.—*Reticulocyte Counts on Normal Adults During Winter and Spring Months*

| Patient | Date | Red Count | Reticulocyte Count | Date | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|---|
| 5 | Jan. 6..... | 4,810,000 | 800 | April 5 | 6,060,000 | 16,000 |
| 31 | Jan. 13..... | 4,860,000 | 400 | April 11 | 5,500,000 | 16,800 |
| 70 | Jan. 6..... | 6,480,000 | 0 | April 11 | 6,050,000 | 3,000 |
| 68 | Jan. 7..... | 6,100,000 | 0 | April 21 | 5,400,000 | 21,000 |
| 29 | Feb. 16..... | 4,940,000 | 600 | April 11 | ..... | 8,400 |
| 30 | Feb. 16..... | 5,410,000 | 800 | April 4 | ..... | 10,000 |
| 32 | March 7..... | 4,020,000 | 1,000 | April 18 | 4,940,000 | 10,000 |
| 34 | March 7..... | 4,680,000 | 1,000 | April 1 | ..... | 21,000 |
| 36 | March 8..... | 5,820,000 | 4,000 | April 9 | ..... | 5,600 |
| 38 | March 8..... | 4,990,000 | 3,000 | April 12 | ..... | 21,000 |
| 39 | March 8..... | 4,120,000 | 2,000 | April 12 | ..... | 11,200 |
| 45 | March 10..... | 5,490,000 | 2,000 | April 29 | 5,620,000 | 4,400 |
| 47 | March 10..... | 5,240,000 | 4,000 | April 9 | ..... | 24,800 |
| 48 | March 11..... | 4,160,000 | 2,800 | April 11 | ..... | 12,000 |
| 51 | March 11..... | 4,970,000 | 2,400 | April 12 | ..... | 6,000 |
| 52 | March 11..... | 3,790,000 | 2,000 | April 12 | ..... | 6,000 |

TABLE 2.—*Repeated Reticulocyte Counts in a Normal Adult*

| Date | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| 3/20/27 ..... | 70 | 5,000 | 4,460,000 | 3,600 |
| 3/21/27 ..... | .. | ..... | ..... | 4,800 |
| 3/22/27 ..... | .. | ..... | ..... | 6,000 |
| 3/25/27 ..... | .. | ..... | ..... | 6,000 |
| 3/28/27 ..... | .. | ..... | ..... | 5,600 |
| 4/13/27 ..... | .. | ..... | ..... | 7,000 |
| 4/20/27 ..... | .. | ..... | ..... | 14,000 |
| 5/ 3/27 ..... | .. | ..... | ..... | 20,000 |
| 5/17/27 ..... | .. | ..... | ..... | 4,000 |
| 5/25/27 ..... | .. | ..... | ..... | 4,800 |
| 6/25/27 ..... | .. | ..... | ..... | 6,000 |
| 7/25/27 ..... | .. | ..... | ..... | 8,800 |
| 10/14/27 ..... | 80 | 6,400 | 4,870,000 | 5,000 |
| 3/ 5/28 ..... | 80 | ..... | 4,680,000 | 6,000 |

1. The counts were invariably higher during the spring months, although even at this time the highest figure obtained was 0.4 per cent (number 47). Our figures, as found during the spring and summer months, check closely with those of Seyfarth.[7] The probable explanation for the increased count during the spring months is that of the general stimulation of the body produced by the increase in ultraviolet rays from the sun at that time. In this connection, it may be noted that check counts done at the Taft heliotherapy ward, at the Cincinnati General Hospital, where both natural and artificial rays are used, showed an increase in the reticulocyte count after heliotherapy. In table 2

are shown the reticulocyte counts on a healthy adult, as found at intervals during a year's time. Tables 3 and 4 show the change in the reticulocyte count in healthy adults from the winter to the spring months.

In connection with these studies and with particular reference to the reticulocyte count in benzene poisoning (which is to be the subject

TABLE 3.—*Repeated Reticulocyte Counts in the Same Person (a Normal Subject), Showing Rise of Reticulocyte Count During the Spring Months*

| Date | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| 1/ 6/26 | 80 | 9,200 | 4,810,000 | 800 |
| 11/19/26 | 90 | 10,000 | 6,060,000 | 6,400 |
| 1/28/27 | .. | ..... | ..... | 400 |
| 3/20/27 | .. | ..... | ..... | 16,000 |
| 3/21/27 | .. | ..... | ..... | 16,800 |
| 4/ 5/27 | .. | ..... | ..... | 16,000 |
| 5/18/27 | 80 | 8,400 | 5,320,000 | 14,200 |

TABLE 4.—*Repeated Reticulocyte Counts in H. W., a Normal Adult, Showing Rise of the Reticulocyte Count During the Spring Months*

| Date | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| 1/13/27 | 75 | ..... | 4,860,000 | 400 |
| 2/16/27 | 70 | 7,000 | 4,640,000 | 1,200 |
| 4/11/27 | .. | ..... | ..... | 16,800 |
| 5/26/27 | 80 | 8,000 | 5,500,000 | 16,400 |
| 11/14/27 | 80 | 9,000 | 4,710,000 | 9,200 |

TABLE 5.—*Reticulocyte Counts on Full-Grown Rabbits* *

| Date | Rabbit Number | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| June 14 | 1 | 16,400 | 5,480,000 | 72,000 |
| June 18 | 2 | 7,600 | 5,440,000 | 40,000 |
| July 7 | 3 | 10,200 | 6,080,000 | 23,200 |
| July 16 | 4 | 16,600 | 5,280,000 | 80,000 |
| July 23 | 5 | 9,200 | 5,440,000 | 34,000 |
| July 24 | 6 | 16,400 | 6,240,000 | 42,000 |
| Dec. 24 | 7 | 7,800 | 5,540,000 | 14,000 |
| Dec. 17 | 8 | 9,800 | 5,120,000 | 29,400 |
| Dec. 12 | 9 | 10,600 | 5,460,000 | 28,000 |
| March 14 | 10 | 8,200 | 5,840,000 | 36,000 |
| March 14 | 11 | 9,400 | 6,280,000 | 18,000 |
| April 2 | 12 | 8,000 | 5,240,000 | 41,000 |

* The reticulocyte counts in rabbits vary within wide limits and are higher than those in normal human beings.

of another paper), we made reticulocyte counts on a number of laboratory animals. In earlier studies on benzene poisoning, the white blood counts on rabbits were used as indexes. We have found that the reticulocyte counts in full grown rabbits are much higher than those in human beings. Furthermore, there is great individual variation. These facts are set forth in table 5.

In guinea-pigs the reticulocyte counts in our studies approximated the figures as found for human beings (table 6).

The counts in monkeys and in dogs were approximately the same as in human beings.

In cats, we found the reticulocyte count to be somewhat lower than it is in human beings (table 7).

TABLE 6.—*Reticulocyte Counts in Normal Full-Grown Guinea-Pigs* *

| Date | Guinea-Pig Number | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| Jan. 23 | 1 | 7,400 | 5,480,000 | 16,000 |
| Jan. 23 | 2 | 8,600 | 6,480,000 | 7,800 |
| Jan. 24 | 3 | 8,200 | 5,600,000 | 8,000 |
| June 28 | 4 | 9,600 | 5,640,000 | 12,800 |
| July 11 | 5 | 12,800 | 6,480,000 | 6,400 |
| July 11 | 6 | 8,900 | 4,960,000 | 8,000 |
| July 11 | 7 | 9,800 | 5,480,000 | 12,400 |
| July 11 | 8 | 14,200 | 5,780,000 | 4,800 |
| June 16 | 9 | 8,000 | 5,360,000 | 5,800 |
| June 16 | 10 | 9,200 | 5,120,000 | 12,600 |
| June 13 | 11 | 9,800 | 5,960,000 | 8,000 |
| Sept. 1 | 12 | 8,600 | 6,160,000 | 9,800 |

* The reticulocyte count in guinea-pigs is similar to that of human beings.

TABLE 7.—*Reticulocyte Counts on Full-Grown Cats* *

| Date | Cat Number | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| June 13 | 1 | 12,800 | 5,400,000 | 800 |
| June 14 | 2 | 9,800 | 5,640,000 | 200 |
| July 11 | 3 | 24,800 | 6,120,000 | 400 |
| July 12 | 4 | 18,800 | 5,520,000 | 1,400 |
| July 14 | 5 | 20,400 | 5,840,000 | 200 |
| Sept. 8 | 6 | 34,000 | 5,720,000 | 2,400 |
| Sept. 1 | 7 | 18,000 | 5,640,000 | 200 |
| Sept. 1 | 8 | 22,000 | 5,880,000 | 200 |
| Sept. 4 | 9 | 10,800 | 6,120,000 | 800 |
| June 14 | 10 | 15,400 | 6,200,000 | 1,400 |

* Cats show a somewhat lower reticulocyte count than human beings.

Our studies would thus have given the following normal averages:

| | |
|---|---|
| Man | 0.03 to 0.2 per cent |
| Rabbit | 0.25 to 1.5 per cent |
| Guinea-pigs | 0.08 to 0.29 per cent |
| Cats | 0.003 to 0.04 per cent |

The foregoing figures may be compared with those of Krumbhaar,[6] who, using a different method of counting, gave the following averages:

| | |
|---|---|
| Man | 0.1 to 0.8 per cent |
| Rabbit | 0.6 to 2.8 per cent |
| Guinea-pigs | 1.0 to 4.0 per cent |
| Cat | 0.0 to 0.4 per cent |

In an earlier paper[5] we showed the physiologic increase in the reticulocyte count in the new-born infant. In table 8, taken from this paper, reticulocyte counts in the new-born infant are shown. These figures check fairly well with the counts of other observers.

TABLE 8.—*Quantitative Estimation of Basophilic Cells to the Cubic Centimeter of Blood in the New-Born Infant. Blood Pipet and Counting Chamber. Polychrome Methylene Blue*

| Sex * | Color | Age | Date and Count | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ♀ | W | 1 hour..... | 2/ 6/25—18,000 | 2/ 7/25—16,400 | 2/ 9/25—14,000 | 2/10/25—11,200 | 2/12/25—6,000 | 2/13—4,300 | 2/14—1,200 | 2/16—250 | 2/17—20 | |
| ♂ | C | 12 hours..... | 2/ 9/25—16,000 | 2/10 —14,000 | 2/11 — 9,400 | 2/12 — 8,800 | 2/13 —4,200 | 2/14—2,000 | 2/16— 270 | 2/17—130 | 2/18—25 | |
| ♀ | W | 12 hours..... | 2/16/25—16,400 | 2/17 —14,000 | 2/18 —11,200 | 2/19 — 7,000 | 2/20 —4,800 | 2/21—2,000 | 2/23— 750 | 2/24— 10 | | |
| ♂ | W | 18 hours..... | 2/17/25—17,000 | 2/18 —15,000 | 2/19 —12,800 | 2/20 — 9,400 | 2/21 —6,400 | 2/23—2,000 | 2/24— 450 | 2/25— 10 | | |
| ♂ | W | 6 hours..... | 3/ 9/25—17,000 | 3/11 —14,400 | 3/13 —11,000 | 3/16 — 4,200 | 3/18 —1,000 | 3/20 20 } Twins | | | | |
| ♂ | W | 6 hours..... | 3/ 9/25—15,800 | 3/11 —13,800 | 3/13 —10,800 | 3/16 — 3,200 | 3/18 — 450 | 3/20 10 } Twins | | | | |
| ♂ | C | 12 hours..... | 3/16/25—14,800 | 3/18 —10,000 | 3/20 — 4,000 | 3/23 — 250 | 3/25 — 10 | | | | | |
| ♂ | W | 7 months..... | 3/16/25—28,400 | 3/18 —20,400 | 3/20 —16,000 | 3/21—Child died | | | | | | |
| Premature, 12 hours after birth | | | | | | Twins | | | | | | |

* In this column, ♀ indicates female; ♂, male.

The reticulocyte count is also increased during pregnancy. Table 9 shows a series of counts in pregnant women. It will be noted that all of these counts were done during the winter months, so that the comparatively slight increase is explained.

TABLE 9.—*Reticulocyte Counts on Pregnant Women* *

| Date | Patient | Month of Pregnancy | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|---|
| Jan. 31 | O. S. | Eighth | 70 | 13,000 | 4,720,000 | 19,400 |
| Jan. 31 | A. F. | Sixth | 70 | 10,000 | 4,450,000 | 8,000 |
| Jan. 31 | R. H. | Seventh | 70 | 10,500 | 4,540,000 | 9,000 |
| Feb. 8 | M. J. | Sixth | 60 | 11,000 | 3,880,000 | 12,800 |
| Feb. 8 | M. L. | Eighth | 60 | 13,000 | 4,450,000 | 18,000 |
| Feb. 8 | J. G. | Fifth | 70 | 10,000 | 4,640,000 | 11,400 |
| Feb. 14 | K. F. | Fifth | 60 | 9,000 | 3,180,000 | 8,400 |
| Feb. 14 | S. H. | Eighth | 70 | 8,000 | 4,820,000 | 10,800 |
| Feb. 14 | K. W. | Eighth | 60 | 10,000 | 3,460,000 | 14,400 |
| March 8 | D. S | Ninth | 65 | 8,000 | 3,950,000 | 15,000 |
| March 7 | F. J. | Eighth | 70 | 8,000 | 4,340,000 | 24,000 |
| March 10 | B. H. | Third | 80 | 8,600 | 5,650,000 | 21,000 |

* The retriculocytes count is somewhat increased during pregnancy.

TABLE 10.—*Blood Counts on Patients with Acute and Chronic Infections and Chronic Diseases*

| Date | Patient | Type of Infection | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|---|
| 11/14 | B. T. | Lobar pneumonia | 65 | 23,000 | 3,530,000 | 7,000 |
| 1/ 8 | L. T. | Lobar pneumonia | 70 | 56,800 | 5,200,000 | 800 |
| 1/12 | W. R. | Lobar pneumonia | 70 | 13,400 | 4,640,000 | 4,400 |
| 4/ 1 | R. B. | Lobar pneumonia | 70 | 18,600 | 4,360,000 | 10,000 |
| 6/18 | H. R. | Bronchopneumonia | 75 | 12,400 | 4,800,000 | 1,800 |
| 3/29 | R. C. | Bronchopneumonia | 75 | 20,000 | 4,710,000 | 800 |
| 12/24 | M. K. | Endocarditis | 60 | 10,200 | 4,510,000 | 10,000 |
| 1/11 | C. M. | Endocarditis | 70 | 10,600 | 3,820,000 | 12,000 |
| 3/24 | B. C. | Endocarditis | 60 | 15,000 | 3,950,000 | 20,000 |
| 6/ 7 | B. R. | Endocarditis | 55 | 8,000 | 2,900,000 | 13,000 |
| 1/ 6 | G. B. | Myocarditis | 70 | 7,400 | 4,690,000 | 400 |
| 1/14 | A. U. | Myocarditis | 70 | 6,500 | 4,360,000 | 0 |
| 1/26 | J. C. | Typhoid | 70 | 4,200 | 4,700,000 | 4,200 |
| 2/26 | L. M. | Typhoid | 75 | 5,600 | 5,120,000 | 6,000 |
| 3/ 3 | J. P. | Multiple arthritis | 80 | 12,400 | 5,630,000 | 1,800 |
| 3/ 3 | R. C. | Multiple arthritis | 75 | 10,000 | 4,490,000 | 0 |
| 3/ 2 | J. M. | Multiple arthritis | 70 | 10,200 | 3,430,000 | 3,000 |
| 12/13 | H. M. | Nephritis, acute | 40 | 7,000 | 1,790,000 | 9,000 |
| 4/ 7 | H. C. | Nephritis, acute | .. | ..... | ..... | 7,400 |
| 5/28 | T. H. | Nephritis, chronic | 85 | 9,000 | 5,400,000 | 16,000 |
| 12/11 | P. B. | Catarrhal jaundice | 75 | ..... | 4,820,000 | 0 |
| 3/23 | H. B. | Catarrhal jaundice | 80 | ..... | 5,100,000 | 800 |
| 4/ 7 | R. L. | Catarrhal jaundice | 80 | ..... | 4,550,000 | 1,400 |
| 6/25 | H. J. | Hanot's cirrhosis | 65 | 5,400 | 3,500,000 | 7,400 |
| 4/23 | F. J. | Carcinoma of the liver | 65 | 11,400 | 4,430,000 | 34,000 |
| 2/16 | A. G. | Syphilitic cirrhosis | 60 | 18,000 | 2,830,000 | 2,200 |
| 4/14 | C. J. | Syphilitic cirrhosis | 65 | 9,800 | 3,930,000 | 7,400 |
| 2/ 8 | D. J. | Pelvic infection (acute) | 75 | 13,400 | 5,190,000 | 11,200 |
| 4/22 | M. J. | Whooping cough | 80 | 21,000 | 6,530,000 | 400 |
| 1/13 | M. R. | Diabetes | 70 | 8,200 | 4,120,000 | 400 |
| 10/29 | G. H. | Eczema | 80 | 7,000 | 4,140,000 | 6,000 |

Studies of the reticulocyte count in a series of patients, at the Cincinnati General Hospital, with acute and chronic infections and with chronic diseases showed comparatively little variation from the normal (table 10). When the condition caused anemia, as in the cases of endocarditis, a slight rise in the reticulocyte count occurred. Of interest

also was the high count in the case of carcinoma of the liver, probably due to the metastases of the bone (verified by autopsy).

We were unable to trace any connection between the white count and the reticulocyte count.

Reticulocyte counts were done on a group of children at the Preventorium of the Cincinnati Municipal Tuberculosis Sanitarium. There was active tuberculosis in the families of these children, for which reason they had been removed to the preventorium. These children were of both sexes, and ranged in age from 5 to 12 years. None of them had active tuberculosis. The reticulocyte counts were all within normal limits (table 11).

TABLE 11.—*Blood Counts in Children in the Tuberculosis Preventorium* *

| Patient | Date | Hemoglobin Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|
| H. F. | 2/14/27 | 80 | 8,000 | 4,720,000 | 1,200 |
| I. R. C. | 2/14/27 | 85 | 9,200 | 4,200,000 | 5,400 |
| M. O. | 2/14/27 | 75 | 5,400 | 3,960,000 | 3,600 |
| P. M. | 2/14/27 | 80 | 7,400 | 4,160,000 | 6,200 |
| E. C. | 2/14/27 | 80 | 8,400 | 4,020,000 | 3,400 |
| O. B. | 2/14/27 | 70 | 5,600 | 3,480,000 | 2,800 |
| J. J. | 2/14/27 | 75 | 5,400 | 3,960,000 | 3,600 |
| C. J. | 2/14/27 | 85 | 5,600 | 4,120,000 | 4,200 |
| I. W. | 2/14/27 | 80 | 6,800 | 4,040,000 | 2,200 |
| L. C. | 2/14/27 | 80 | 6,200 | 4,080,000 | 6,800 |
| I. W. | 2/14/27 | 70 | 7,200 | 3,440,000 | 3,400 |
| A. L. W. | 2/14/27 | 85 | 8,400 | 4,380,000 | 4,200 |
| S. S. | 2/14/27 | 75 | 4,800 | 3,960,000 | 4,400 |
| B. S. | 2/14/27 | 85 | 7,800 | 4,560,000 | 5,400 |
| A. S. | 2/14/27 | 90 | 6,200 | 4,560,000 | 5,200 |
| T. W. | 2/14/27 | 80 | 7,400 | 4,200,000 | 2,200 |
| H. C. | 2/14/27 | 80 | 6,600 | 4,080,000 | 2,200 |
| M. D. | 2/14/27 | 85 | 5,400 | 4,220,000 | 1,200 |
| M. K. | 2/14/27 | 75 | 11,400 | 3,880,000 | 2,000 |
| D. B. | 2/14/27 | 80 | 5,800 | 3,840,000 | 1,800 |
| C. B. | 2/14/27 | 75 | 7,400 | 3,760,000 | 4,400 |
| J. B. | 2/14/27 | 80 | 5,200 | 3,970,000 | 2,000 |
| M. D. | 2/14/27 | 85 | 7,600 | 4,160,000 | 3,600 |
| E. S. | 2/14/27 | 95 | 6,800 | 5,160,000 | 4,800 |
| M. C. | 2/14/27 | 90 | 7,000 | 4,350,000 | 4,800 |

* These counts were done on children from the ages of 5 to 12, who were at the Cincinnati Tuberculosis Sanitarium because members of their families had active tuberculosis. There were no active cases in this group.

Counts were done on adults with active tuberculosis; they were all patients at the Cincinnati Municipal Tuberculosis Sanitarium. The results from experiments on twenty-five patients are shown in table 12. The counts were normal in all but three patients who had tuberculosis of the spine, associated diabetes and recent pulmonary hemorrhage, respectively.

*Lead Poisoning.*—Lead, as is generally known, causes an increase in the reticulocytes and in the production of stippled cells. Stippled cells are probably reticulocytes which have been affected by the toxic substance, lead, in such a way that the granules are much heavier than the granules of normal reticulocytes, so that they can be seen when stained by Wright's stain (or similar stains), without having been vitally stained previously. The term "basophilic degeneration" is well

suited to this condition. It should be remembered, however, that blood which shows stippled cells when stained with Wright's stain will show a much larger number of reticulocytes when stained with brilliant cresyl blue.

The reticulocyte count in lead poisoning and in lead absorption has been made the subject of special study by McCord.[11] He has worked out the details of a test (based on the reticulocyte count) which reveals the degree of lead absorption in workers exposed and permits the institution of preventive measures before actual lead poisoning has taken place. Working in conjunction with McCord to secure, if possible, check results of his test, we ran two series of counts.

TABLE 12.—*Blood Counts on Tuberculous Patients* *

| Patient | Date | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count | |
|---|---|---|---|---|---|---|
| J. S. | 2/16/27 | 80 | 6,800 | 4,240,000 | 1,000 | |
| R. O. | 2/16/27 | 85 | 8,000 | 4,380,000 | 2,800 | |
| J. St. | 2/16/27 | 70 | 7,400 | 3,920,000 | 16,400 | Tuberculosis of spine |
| H. C. | 2/16/27 | 85 | 7,800 | 4,240,000 | 5,800 | No pulmonary tuberculosis |
| C. P. | 2/16/27 | 75 | 9,400 | 3,960,000 | 10,800 | Tuberculosis plus diabetes |
| C. M. | 2/16/27 | 85 | 5,200 | 4,920,000 | 2,200 | |
| W. W. | 2/16/27 | 90 | 8,600 | 5,440,000 | 2,800 | |
| L. M. | 2/16/27 | 90 | 10,200 | 5,240,000 | 400 (repeated) | No sputum |
| M. S. | 2/16/27 | 80 | 8,800 | 4,020,000 | 2,200 | |
| E. P. | 2/16/27 | 85 | 7,400 | 4,380,000 | 3,600 | |
| A. S. | 2/16/27 | 70 | 5,200 | 3,600,000 | 4,200 | |
| A. St. | 2/16/27 | 85 | 8,200 | 5,020,000 | 2,000 | Sputum negative |
| J. S. | 2/16/27 | 65 | 11,400 | 3,480,000 | 16,200 | Recent hemorrhage |
| D. A. | 2/18/27 | 80 | 6,000 | 4,120,000 | 1,600 | |
| C. S. | 2/18/27 | 90 | 5,800 | 5,500,000 | 1,400 | |
| W. D. | 2/18/27 | 80 | 6,200 | 5,060,000 | 3,600 | |
| E. M. | 2/18/27 | 95 | 8,400 | 4,900,000 | 1,800 | |
| A. J. | 2/18/27 | 80 | 8,000 | 4,940,000 | 2,400 | |
| T. H. | 2/18/27 | 85 | 9,600 | 4,160,000 | 1,000 | |
| J. W. | 2/18/27 | 70 | 12,800 | 3,440,000 | 600 | |
| H. C. | 2/18/27 | 80 | 5,800 | 4,080,000 | 1,000 | Tuberculosis of spine |
| L. H. | 2/18/27 | 60 | 9,200 | 3,160,000 | 1,800 | |
| W. L. R. | 2/18/27 | 85 | 6,400 | 4,200,000 | 1,600 | Pneumothorax |
| L. R. | 2/18/27 | 80 | 5,200 | 4,160,000 | 2,400 | |
| W. Q. | 2/18/27 | 70 | 8,800 | 3,680,000 | 3,800 | Tuberculosis; laryngitis |

* The counts were done on adult patients with active tuberculosis. All were patients in the Municipal Tuberculosis Sanitarium.

In the first series, table 13, we studied twenty-five normal adults who were working in the offices of lead factories, but who were not directly exposed to the lead hazard. In all except one of these persons (patient 63), the reticulocyte count was normal. The patient in whom the count was not normal was a man who had previously worked in the factory in direct contact with lead.

Table 14 shows the high reticulocyte count in persons working in lead factories, even though they showed no clinical symptoms of lead poisoning.

Lead is not the only heavy metal which causes an increased reticulocyte count. In mercury poisoning the reticulocyte count also goes up, though the rise is not so marked as that seen in lead poisoning. In

11. McCord (footnote 8, second reference).

table 15 are shown the counts in four patients who had taken large doses of corrosive mercuric chloride.

Hemorrhage is usually a stimulus to regeneration of the blood, as shown by an increase in the reticulocyte count. In the cases reported in table 16, many reticulocyte counts were done on each patient, but

TABLE 13.—*Blood Counts on Normal Adults Working in the Offices of Lead Factories* *

| Patient Number | Date | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|
| 57 | 11/ 5/26 | 85 | 13,200 | 5,120,000 | 9,600 |
| 58 | 11/ 5/26 | 75 | 9,600 | 4,760,000 | 4,800 |
| 59 | 11/ 5/26 | 80 | 8,800 | 4,920,000 | 3,200 |
| 60 | 11/ 5/26 | 80 | 11,800 | 5,120,000 | 3,000 |
| 61 | 11/ 5/26 | 85 | 13,600 | 5,240,000 | 200 |
| 62 | 11/ 5/26 | 80 | 8,200 | 5,160,000 | 1,000 |
| 63 | 11/ 5/26 | 85 | 9,400 | 5,080,000 | 18,400 |
| 64 | 11/ 5/26 | 80 | 9,200 | 4,880,000 | 4,000 |
| 66 | 11/ 5/26 | 85 | 14,200 | 5,280,000 | 400 |
| 67 | 11/ 5/26 | 85 | 8,800 | 5,360,000 | 1,800 |
| 68 | 11/ 5/26 | 75 | 10,800 | 4,560,000 | 7,000 |
| 69 | 11/ 5/26 | 85 | 9,400 | 5,280,000 | 600 |
| 71 | 11/12/26 | 90 | 7,600 | 5,160,000 | 600 |
| 72 | 11/12/26 | 75 | 11,400 | 3,960,000 | 3,800 |
| 73 | 11/12/26 | 80 | 12,400 | 4,240,000 | 2,600 |
| 74 | 11/12/26 | 75 | 11,400 | 4,040,000 | 2,200 |
| 75 | 11/12/26 | 65 | 12,000 | 3,760,000 | 2,400 |
| 76 | 11/12/26 | 80 | 10,600 | 4,360,000 | 1,400 |
| 77 | 11/12/26 | 85 | 9,200 | 4,600,000 | 600 |
| 78 | 11/12/26 | 90 | 9,200 | 5,280,000 | 800 |
| 79 | 11/12/26 | 85 | 9,200 | 4,880,000 | 9,200 |
| 80 | 11/12/26 | 90 | 10,800 | 5,040,000 | 1,400 |
| 81 | 11/12/26 | 95 | 9,800 | 5,560,000 | 800 |
| 82 | 11/12/26 | 85 | 8,200 | 4,820,000 | 400 |
| 83 | 11/12/26 | 80 | 7,800 | 4,420,000 | 400 |

* These patients had no contact with any form of lead, except one patient, number 63, who had previously worked in the factory and had had an attack of lead poisoning.

TABLE 14.—*Blood Counts on Persons Working with Lead*

| | | | | | | Differential Count | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Date | Patient | Hemoglobin, per Cent | White Count | Red Count | Reticulocyte Count | Polymorphonuclears | Lymphocytes | Mononuclears | Eosinophils | Basophils |
| 11/ 5 | W. O. | 60 | 11,400 | 3,440,000 | 32,000 | 48 | 47 | 2 | 3 | 0 |
| 10/19 | J. N. | 80 | 12,400 | 4,280,000 | 12,400 | 50 | 37 | 8 | 2 | 0 |
| 10/22 | F. D. | 70 | 10,600 | 3,920,000 | 70,400 | 51 | 46 | 1 | 2 | 0 |
| 10/22 | L. J. | 70 | 9,800 | 3,840,000 | 22,000 | 57 | 39 | 3 | 0 | 1 |
| 10/22 | C. K. | 85 | 11,400 | 5,320,000 | 44,800 | 52 | 45 | 3 | 0 | 0 |
| 10/22 | W. A. | 65 | 9,200 | 3,640,000 | 61,600 | 48 | 48 | 1 | 3 | 0 |
| 11/ 5 | M. D. | 85 | 9,400 | 5,080,000 | 18,400 | 61 | 38 | 1 | 0 | 0 |
| 10/22 | G. A. | 80 | 12,400 | 4,840,000 | 68,600 | 49 | 46 | 1 | 4 | 0 |

only the maximum reticulocyte count is shown in the table. The time at which the maximum is reached varies with the amount of hemorrhage and the period of time over which it has extended. It is usually reached about five days after the bleeding has stopped. The red cell count then begins to rise, and as it approaches normal the reticulocyte count drops.

To a certain degree, the reticulocyte count affords a prognostic index as to whether regeneration of the blood will proceed normally

after hemorrhage has stopped, or as to whether stimulation to regeneration of the blood, as by transfusion, is needed.

In table 17 we show counts in four cases of bleeding duodenal ulcer. These patients were all in the medical service of the Cincinnati General Hospital. All of them presented the classic symptoms of duodenal ulcer, with characteristic roentgen observations. All of them had tarry stools. In two of these patients (W. A. and E. E., table 17), the reticulocyte count did not rise after the bleeding had stopped. One patient, W. A., had 1,880,000 red cells with 13,400 reticulocytes. He was given a transfusion of 500 cc. of blood, with a prompt rise in the

TABLE 15.—*Counts on Patients with Corrosive Mercuric Chloride Poisoning*

| Date | Patient | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|
| 12/23 | J. J. | 90 | 51,000 | 6,480,000 | 14,000 |
| 1/17 | M. D. | 75 | 120,000 | 5,510,000 | 18,000 |
| 12/29 | E. M. | 80 | 9,000 | 4,940,000 | 33,600 |
| 12/20 | H. K. | 85 | 17,000 | 6,000,000 | 16,000 |

TABLE 16.—*Reticulocyte Counts on Patients After Hemorrhage*

| Date | Patient | Hemorrhage From | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count * |
|---|---|---|---|---|---|---|
| 4/ 5 | L. M. | Duodenal ulcer | 40 | 7,000 | 2,380,000 | 64,000 |
| 4/27 | M. T. | Epistaxis | 50 | 5,400 | 2,400,000 | 57,000 |
| 1/25 | J. M. | Ulcerative colitis | .. | ..... | 2,780,000 | 80,000 |
| 11/26 | D. H. | Tooth extraction | 40 | ..... | 2,120,000 | 64,000 |
| 12/ 2 | W. A. | Duodenal ulcer | 60 | 7,000 | 3,150,000 | 63,000 |
| 12/23 | R. M. | Duodenal ulcer | .. | ..... | 3,560,000 | 84,800 |
| 12/18 | J. L. | Duodenal ulcer | .. | ..... | 3,540,000 | 39,600 |
| 1/25 | H. M. | Nose and gums | .. | ..... | 1,010,000 | 52,000 |
| 2/25 | V. W. | Gastric ulcer | .. | ..... | 2,230,000 | 44,000 |
| 2/26 | G. T. | Tooth extraction | .. | ..... | 3,760,000 | 40,000 |
| 4/ 7 | J. S. | Duodenal ulcer | .. | ..... | 2,980,000 | 226,000 |
| 1/28 | C. W. | Duodenal ulcer | .. | ..... | 1,770,000 | 100,000 |
| 4/29 | E. W. | Telangiectasis | .. | ..... | 3,200,000 | 112,000 |
| 10/24 | L. W. | Gastric ulcer | 60 | 4,000 | 2,900,000 | 320,000 |
| 12/11 | P. N. | Bleeding from gums and bowel | .. | ..... | 1,320,000 | 7,200 |

* In each of the cases many counts were done, but only the maximum reticulocyte count has been included in the table.

reticulocyte count, followed in five days by a marked rise in the red cell count, which was maintained after the reticulocyte count dropped.

Another patient, E. E., had 2,560,000 red cells with a reticulocyte count of 8,400. After a transfusion of 500 cc., the reticulocyte count rose, followed in six days by a rise in the red cell count, which was maintained until the patient was discharged.

In two other cases, R. M. and L. W., the reticulocyte count was found to be high after bleeding had stopped. Accordingly, we advised that transfusion was unnecessary. The reticulocyte count in each instance continued to rise, the red cell count came up and was maintained even after the reticulocyte count had dropped. The figures for the four cases are tabulated in table 17.

The amount of blood loss which is necessary to cause a rise in the reticulocyte count evidently varies with the general condition of the patient. Thus, a hemorrhage of 600 cc. in healthy man produced no appreciable change in the reticulocyte count (table 18). This man gave 600 cc. of blood for a transfusion, without marked change in either the red cell or the reticulocyte count.

TABLE 17.—*Reticulocyte Counts on Four Patients with Duodenal Ulcer*

| W. A., White, Male, Aged 27 | | | | E. E., White, Male, Aged 43 | | | |
|---|---|---|---|---|---|---|---|
| Date | Hemoglobin, Per Cent | Red Blood Cells | Reticulocytes | Date | Hemoglobin, Per Cent | Red Blood Cells | Reticulocytes |
| 11/26 | 40 | 1,880,000 | 13,400 | 2/ 3 | 50 | 2,056,000 | 8,400 |
| 11/27 | .. | Transfusion of 500 cc. of blood | | 2/ 4 | .. | Transfusion of 500 cc. of blood | |
| 11/28 | .. | ..... | 20,200 | 2/ 5 | .. | 2,540,000 | 88,800 |
| 11/30 | .. | ..... | 48,000 | 2/11 | .. | 2,680,000 | 70,000 |
| 12/ 1 | .. | ..... | 63,000 | 2/16 | .. | 3,390,000 | 64,000 |
| 12/ 2 | .. | ..... | 59,400 | 3/ 1 | .. | 3,790,000 | 34,000 |
| 12/ 3 | 50 | 3,150,000 | 53,200 | 3/ 4 | 60 | 3,840,000 | 14,000 |
| 12/ 4 | .. | ..... | 54,000 | 3/ 8 | .. | 4,030,000 | 2,000 |
| 12/ 5 | .. | ..... | 54,800 | 3/16 | 70 | 4,100,000 | 2,400 |
| 12/ 7 | .. | 3,110,000 | 55,000 | 3/18 | .. | Discharged | ..... |
| 12/ 8 | .. | ..... | 51,000 | ..... | .. | ..... | ..... |
| 12/ 9 | 65 | 3,990,000 | 38,400 | ..... | .. | ..... | ..... |
| 12/11 | .. | Discharged | ..... | ..... | .. | ..... | ..... |

| R. M., White, Male, Aged 45 | | | | L. W., White, Male, Aged 23 | | | |
|---|---|---|---|---|---|---|---|
| Date | Hemoglobin, Per Cent | Red Blood Cells | Reticulocytes | Date | Hemoglobin, Per Cent | Red Blood Cells | Reticulocytes |
| 12/11 | 40 | 2,390,000 | 42,400 | 10/20 | 45 | 2,000,000 | 109,200 |
| 12/18 | .. | 2,780,000 | 84,800 | 10/24 | 60 | 2,900,000 | 320,000 |
| 12/23 | .. | 3,560,000 | 84,800 | 10/29 | 70 | 3,860,000 | 160,000 |
| 12/28 | 60 | 3,680,000 | 39,200 | 11/ 5 | 75 | 4,130,000 | 28,400 |
| 12/30 | .. | Discharged | ..... | 11/ 7 | .. | Discharged | ..... |

TABLE 18.—*Reticulocyte Count on a Healthy Man Following Hemorrhage* *

| Date | Red Count | Reticulocyte Count |
|---|---|---|
| 4/27/26 | 5,200,000 | 2,000 |
| 4/28/26 | Hemorrhage of 600 cc. of blood | |
| 4/28/26 | 5,220,000 | 2,000 |
| 4/29/26 | 5,180,000 | 5,000 |
| 4/30/26 | 5,200,000 | 2,000 |
| 5/ 1/26 | 5,080,000 | 2,200 |
| 5/ 2/26 | 5,240,000 | 4,800 |
| 5/ 4/26 | 5,400,000 | 4,200 |
| 5/ 7/26 | 5,360,000 | 3,000 |

* D. H., a healthy man, gave 600 cc. of blood for a transfusion. There was no appreciable change in either the red or the reticulocyte count.

On the other hand, a much smaller blood loss caused a definite rise in the reticulocyte count in a tuberculous patient (table 19). J. K., a patient at the Cincinnati Tuberculosis Sanitarium, had a pulmonary hemorrhage of about 200 cc. The hemorrhage produced a rise in the reticulocyte count, which reached its maximum seven days after the hemorrhage had occurred.

Patients with blood dyscrasias, other than pernicious anemia, show marked variation in their reticulocyte counts. Single counts on a group of patients with such disorders are shown in table 20.

Patients with familial hemolytic jaundice and with sickle cell anemia show high reticulocyte counts at all times.

Patients with hemolytic jaundice (not familial) show some increase in the reticulocyte count, while patients with obstructive jaundice do not. This fact may at times afford a differential diagnostic index of some value. We also noted that the reticulocyte count in acute leukemia

TABLE 19.—*The Red and Reticulocyte Counts on a Tuberculous Patient Following Hemorrhage*

| Date | Hemoglobin, Per Cent | Red Count | Reticulocyte Count | |
|---|---|---|---|---|
| 1/ 4/27 | 70 | 3,880,000 | 6,200 | Six ounce hemorrhage |
| 1/ 5/27 | .. | 3,960,000 | 8,600 | Sputum bloody |
| 1/ 6/27 | 70 | 3,760,000 | 7,800 | Sputum bloody |
| 1/ 7/27 | .. | 3,640,000 | 10,400 | Sputum blood streaked |
| 1/ 8/27 | 75 | 3,760,000 | 21,000 | Sputum blood streaked |
| 1/ 9/27 | .. | 3,560,000 | 18,000 | Sputum blood streaked |
| 1/10/27 | 70 | 3,280,000 | 22,000 | Sputum blood streaked |
| 1/11/27 | .. | 3,560,000 | 28,000 | Sputum free from blood |
| 1/12/27 | 70 | 3,320,000 | 20,000 | Sputum free from blood |
| 1/13/27 | .. | 3,760,000 | 16,000 | Sputum free from blood |
| 1/14/27 | 75 | 3,560,000 | 11,000 | Sputum free from blood |
| 1/16/27 | .. | 3,560,000 | 11,000 | Sputum free from blood |
| 1/18/27 | 70 | 3,600,000 | 12,000 | Sputum free from blood |
| 1/20/27 | .. | 3,440,000 | 10,000 | Sputum free from blood |
| 1/22/27 | 70 | 3,640,000 | 10,000 | Sputum free from blood |
| 1/14/27 | .. | 3,880,000 | 10,000 | Sputum free from blood |
| 1/26/27 | 70 | 3,800,000 | 7,000 | Sputum free from blood |
| 1/28/27 | .. | 3,840,000 | 8,000 | Sputum free from blood |

TABLE 20.—*Reticulocyte Counts on Patients with Diseases of the Blood Other than Pernicious Anemia*

| Date | Patient | Disease | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|---|
| 6/ 1 | T. S. | Malaria | .. | ..... | 3,400,000 | 94,000 |
| 2/15 | J. A. | Hemophilia | 75 | 8,200 | 4,430,000 | 800 |
| 12/ 4 | D. H. | Hemophilia | 70 | ..... | 4,240,000 | 4,000 |
| 2/11 | H. P. | Hemolytic jaundice | 75 | 7,000 | 4,850,000 | 20,000 |
| 3/21 | M. N. | Familial jaundice | .. | 18,000 | 4,600,000 | 220,000 |
| 4/23 | L. S. | Purpura | .. | ..... | 3,960,000 | 20,000 |
| 4/27 | M. T. | Purpura | 50 | 5,400 | 2,400,000 | 57,000 |
| 3/14 | J. M. | Lymphatic leukemia (acute) | 30 | 46,000 | 1,120,000 | 4,800 |
| 4/14 | R. R. | Lymphatic leukemia (chronic) | .. | 90,000 | 3,420,000 | 8,200 |
| 11/29 | M. S. | Myelogenous leukemia (acute) | 30 | 96,800 | 1,110,000 | 1,800 |
| 12/ 5 | J. K. | Myelogenous leukemia (chronic) | 60 | 80,400 | 3,030,000 | 126,000 |
| 12/16 | L. S. | Myelogenous leukemia (chronic) | 60 | 510,000 | 2,010,000 | 35,600 |
| 11/16 | C. B. | Sickle cell anemia | .. | 7,200 | 4,650,000 | 313,600 |
| 3/19 | A. L. | Sickle cell anemia | .. | 24,800 | 2,980,000 | 416,000 |
| 3/17 | L. B. | Von Jaksch's anemia | 40 | 9,800 | 2,960,000 | 71,000 |
| 11/20 | A. B. | Polycythemia | 120 | ..... | 7,840,000 | 400 |

is apt to be low. In chronic leukemia the reticulocyte count may offer an aid to prognosis. When the count is high, the patient will probably have a remission; when it is low, there is apt to be a relapse.

Cases of hemophilia show a rise in the reticulocyte count only after hemorrhage.

Cases of polycythemia show a low reticulocyte count.

*Pernicious Anemia.*—The value of the reticulocyte count as an index to regeneration of the blood has been so thoroughly attested that it is

now generally accepted. It has been used as a check test to determine the potency of particular kinds of liver extract, or of the variable potency of various batches of extract made by the same process.[12]

Table 21 shows the reticulocyte counts on patients with pernicious anemia shortly after admission to the Cincinnati General Hospital, before any method of treatment had been instituted. It will be seen that the counts vary greatly, and that before treatment the reticulocyte count and the red cell count do not always stand in direct proportion.

Thus, one patient, G. S., showed 3,596,000 red cells, with only 6,800 reticulocytes. Another patient, F. S., had 1,460,000 red cells, with 256,000 reticulocytes.

What can be asserted is that patients with high reticulocyte counts are soon to have a remission, those with low counts, a relapse, unless

TABLE 21.—*Reticulocyte Counts on Patients with Pernicious Anemia* *

| Date | Patient | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|
| 4/20 | M. H. | 40 | 1,700 | 1,648,000 | 12,000 |
| 5/ 4 | L. M. | 70 | 4,400 | 2,933,000 | 11,800 |
| 4/20 | G. S. | 100 | 5,250 | 3,596,000 | 6,800 |
| 5/ 5 | C. K. | 30 | ..... | 1,208,000 | 1,400 |
| 3/24 | M. K. | 100 | ..... | 3,008,000 | 9,000 |
| 6/14 | C. T. | 30 | 6,500 | 1,064,000 | 12,000 |
| 1/11 | L. Mc. | 30 | 4,800 | 1,330,000 | 14,600 |
| 5/26 | M. D. | 70 | 5,600 | 3,370,000 | 36,000 |
| 2/24 | M. K. | 75 | 4,400 | 3,580,000 | 6,000 |
| 3/24 | F. S. | 30 | 4,400 | 1,460,000 | 256,000 |
| 5/ 6 | M. F. | 60 | 3,600 | 2,150,000 | 8,000 |
| 6/16 | C. C. | .. | 1,500 | 1,840,000 | 23,000 |
| 5/ 5 | M. B. | 40 | 3,600 | 1,730,000 | 52,800 |
| 5/17 | S. R. | .. | ..... | 1,500,000 | 18,000 |
| 3/27 | D. N. | 30 | 2,800 | 780,000 | 13,600 |

* The counts were made immediately after admission to the hospital before any type of treatment was instituted.

treatment is instituted. We have been able to confirm this general hypothesis in the cases studied so far.

Furthermore, if after any method of treatment such as transfusion, heliotherapy, injections of arsenic, etc., the reticulocyte count does not show a rather prompt and marked increase, the probabilities are against the onset of a remission.

While it is true that in some cases an increase in the reticulocyte count (and later in the red cell count) did follow the institution of treatment by one or another of the means noted, it is also true that in no case was the rise so high as it was after the use of liver extract.

It is now a matter of general observation that patients with pernicious anemia respond better to the administration of liver extract than to any other method of treatment. This applies both to blood counts and to general clinical improvement.

12. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: Am. J. M. Sc. **175**:581, 1928.

Table 22 gives the maximum reticulocyte counts done on patients with pernicious anemia treated with liver extract.

These maximum counts were reached in from seven to nineteen days after the initial dose. The rise in the reticulocyte counts, of course, begins much earlier. Three vials of Lilly's extract were given to each patient daily. So far we have found no case in which the diagnosis of

TABLE 22.—*Reticulocyte Counts on Patients with Pernicious Anemia Who Were Given Liver Extract* *

| Date | Patient | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|---|
| 12/21 | A. B. | 50 | 5,000 | 2,170,000 | 582,000 |
| 1/17 | H. R. | 40 | 1,600 | 1,480,000 | 329,000 |
| 1/24 | H. P. | 40 | 5,000 | 1,800,000 | 240,000 |
| 4/16 | M. P. | 40 | 2,550 | 1,470,000 | 289,000 |

* The patients were given one vial of Lilly's Liver Extract three times daily.

TABLE 23.—*Reticulocyte Counts on A. B., a Patient with Pernicious Anemia, Who Was Given Liver Extract*

| Date | Hemoglobin, Per Cent | White Count | Red Count | Reticulocyte Count |
|---|---|---|---|---|
| 12/27/27 | 40 | 2,800 | 1,300,000 | 7,500 |
| 12/14/27 | .. | ..... | 1,430,000 | 18,400 |
| 12/15/27 | .. | ..... | 1,540,000 | 34,400 |
| 12/16/27 | 50 | 5,000 | 1,490,000 | 42,000 |
| 12/17/27 | .. | ..... | 1,730,000 | 170,000 |
| 12/18/27 | .. | ..... | 1,720,000 | 297,600 |
| 12/19/27 | .. | ..... | 1,850,000 | 363,200 |
| 12/20/27 | .. | ..... | 2,090,000 | 455,000 |
| 12/21/27 | .. | ..... | 2,170,000 | 582,000 |
| 12/22/27 | 60 | 4,000 | 2,270,000 | 489,000 |
| 12/23/27 | .. | ..... | 2,500,000 | 409,000 |
| 12/24/27 | .. | ..... | 2,420,000 | 320,000 |
| 12/26/27 | .. | ..... | 2,450,000 | 118,000 |
| 12/27/27 | .. | ..... | 2,390,000 | 123,000 |
| 12/28/27 | .. | ..... | 2,340,000 | 80,000 |
| 12/29/27 | 65 | 5,600 | 2,550,000 | 40,000 |
| 12/30/27 | .. | ..... | 2,670,000 | 42,000 |
| 12/31/27 | .. | ..... | 2,600,000 | 41,000 |
| 1/ 2/28 | .. | ..... | 2,780,000 | 44,000 |
| 1/ 4/28 | .. | ..... | 2,990,000 | 41,000 |
| 1/ 5/28 | 70 | 8,000 | 3,260,000 | 40,800 |
| 1/ 7/28 | .. | ..... | 3,540,000 | 31,200 |
| 1/10/28 | 75 | ..... | 4,120,000 | 14,000 |
| 1/12/28 | .. | ..... | 4,180,000 | 11,200 |
| 1/14/28 | .. | ..... | 4,350,000 | 8,400 |
| 1/16/28 | 80 | ..... | 4,600,000 | 6,400 |
| 1/23/28 | 80 | 8,000 | 5,420,000 | 2,000 |
| 2/21/28 | 90 | 10,000 | 5,610,000 | 3,200 |
| 3/22/28 | 95 | 7,000 | 6,010,000 | 4,000 |
| 4/26/28 | 90 | 10,000 | 6,180,000 | 21,600 |
| 5/31/28 | 95 | 10,600 | 6,010,000 | 5,200 |

pernicious anemia was certain, in which the patient did not respond to liver extract with a high reticulocyte count, followed by a rise in the red cell count. As the red cell count reaches its maximum, the reticulocyte count drops back to normal.

The rate of increase in counts and the time intervals after the administration of liver extract in pernicious anemia are shown in table 23. The patient in table 23 presented the typical picture of pernicious anemia. The general improvement of his condition kept pace with the improvement in his blood picture.

## COMMENT AND SUMMARY

A clinical method for the accurate counting of the reticulocytes is given. The method is simple, easy to use and enables a worker to count the reticulocytes rapidly and accurately.

We are convinced that the figures for the reticulocyte count as often given are much too high. Such figures as 1 to 1.5 per cent of the red cells in normal persons are incorrect.

Our studies would indicate that the reticulocyte count in normal healthy adults will run from 0.03 to about 0.2 per cent. In other words, the reticulocyte count in the normal healthy adult does not exceed 10,000 per cubic millimeter.

It also seems established that there is a definite increase in the reticulocyte count in healthy persons during the spring months as contrasted with that during the winter months. By our method check counts on the same normal persons ran consistently lower than did counts on the same persons done by other less accurate quantitative methods. The seasonal variation of the count is fairly definite, as shown by various studies.

The higher count during the spring months probably results from the stimulation of the body produced by the increase in ultraviolet rays from the sun at that time. In this connection, it is of interest to note that check counts done at the Taft heliotherapy ward, at the Cincinnati General Hospital, where both natural and artificial rays are used, showed an increase in the reticulocyte count after heliotherapy.

Studies on laboratory animals showed certain definite trends. Counts on rabbits showed great variations, though the counts are much higher than those in human beings.

Cats show lower reticulocyte counts than do human beings. The counts for guinea-pigs, dogs and monkeys approximated those for man.

Physiologic increase in the reticulocyte count is found, as we had previously demonstrated, in the new-born infant. There is also an increase during pregnancy.

Studies on a series of patients with acute and chronic infections and with chronic diseases showed comparatively little variation from the normal, unless there was a complicating anemia. We were unable to trace any connection between the white cell count and the reticulocyte count.

Counts made for a group of patients with active pulmonary tuberculosis showed no marked abnormalities. In a group of children at the Preventorium of the Cincinnati Municipal Tuberculosis Sanitarium, all without active pulmonary tuberculosis, the counts were within normal limits.

Counts on a group of workers in lead factories, who showed no clinical symptoms of lead poisoning, all ran high. Per contra, counts on persons in the offices of these factories, who were not directly exposed to the lead hazard, were within normal limits.

As is known, lead is not the only heavy metal exposure to which causes a high reticulocyte count. Four cases of corrosive mercuric chloride poisoning are reported, all of the patients showing high counts.

The effect of hemorrhage on the reticulocyte count was studied with particular care. Hemorrhage is, of course, usually a stimulus to regeneration of blood, as shown by the increase in the reticulocyte count. The time at which the maximum reticulocyte count is reached varies with the amount of the hemorrhage. It is normally reached about five days after the bleeding has stopped. The red cell count then begins to rise and as it approaches normal, the reticulocyte count drops.

To a certain extent we feel that the reticulocyte count affords a prognostic index as to whether regeneration of the blood will proceed normally after hemorrhage has stopped, or whether induced stimulation, as by transfusion, is needed. Illustrative cases of bleeding duodenal ulcers, both types, are reported.

Studies were also made on patients with blood dyscrasias other than pernicious anemia. Marked variation in the reticulocyte counts in various conditions was found. Patients with familial hemolytic jaundice and with sickle cell anemia show high reticulocyte counts at all times. Patients with hemolytic jaundice (not familial) show some increase in the reticulocyte count, while patients with obstructive jaundice do not. This may, at times, afford a differential diagnostic index of some value. We found that the reticulocyte count in acute leukemia is apt to be low. In chronic leukemia, the reticulocyte count may offer an aid to prognosis. When the count is high, the patient will probably have a remission; when it is low, there is apt to be a relapse. Cases of hemophilia show a rise in the count only after hemorrhage. Cases of polycythemia show a low reticulocyte count.

The value of the reticulocyte count as an index to the regeneration of blood in pernicious anemia has been so thoroughly attested that it is now generally accepted. It has been used as a check test to determine the potency of particular kinds of liver extract made by the same process. It may also be asserted that patients with high reticulocyte counts are soon to have a remission, those with low counts a relapse (unless treatment is instituted). We were also able to compare results in pernicious anemia in patients treated with liver extract and in others treated with transfusion, arsenic, heliotherapy and other remedies. The general observation that patients with pernicious anemia respond better to liver extract than to any other method of treatment was confirmed

by these studies. This applies both to red cell counts and to general clinical improvement.

So far we have found no case in which the diagnosis of pernicious anemia was certain in which the patient did not respond to the administration of liver extract with a high reticulocyte count followed by a rise in the red cell count. As the red cell count reaches its maximum, the reticulocyte count drops back to normal.

# THE VARIABILITY OF BLOOD PRESSURE

## II. A STUDY OF SYSTOLIC PRESSURE AT FIVE MINUTE INTERVALS *

H. S. DIEHL, M.D.
AND
H. D. LEES, M.D. (Tor.)
MINNEAPOLIS

Our recent study of the variability of blood pressure from day to day [1] immediately suggested other questions, such as the amount of time necessary for significant variations of blood pressure to occur and the relation of physical activity to variability of blood pressure. With the hope of throwing some light on these questions we undertook the present study.

### METHODS OF INVESTIGATION

Since our purpose in this study was to observe the variability of blood pressure with the factors of physical activity and long intervals of time kept constant, it was decided to take readings at five minute intervals with the subject inactive throughout. One hundred men students at the University of Minnesota were selected for the study; each student sat quietly at the side of a table, while blood pressure readings were taken at five minute intervals over a period of one hour. The arm band was adjusted at the beginning of the hour and was left in place till the last reading was completed. Mercury instruments and the auscultatory method were utilized throughout. Several physicians of the Health Service staff made the observations, but the same technic was employed by each one. Furthermore, in order to avoid variations due to pressure changes at different times of the day, all readings were taken between 1:30 and 3:30 p. m.

### ANALYSIS OF GROUP STUDIED

The group studied consisted of 100 freshmen of the University of Minnesota unselected except that they were all presumably in normal physical condition. The records of the physical examinations which had been performed on these students at the beginning of the current school year were taken as the basis for judging the students normal.

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* Submitted for publication, Feb. 6, 1929.

* From the Students' Health Service and the Department of Preventive Medicine, the University of Minnesota.

* This study was carried on with the aid of a grant from the Research Fund of the University of Minnesota.

1. Diehl, H. S.: The Variability of Blood Pressure: Morning and Evening Studies, Arch. Int. Med. **43**:835 (June) 1929.

The mean age of the group, at the time of the examination, was 20.16± 0.14 years; the mean height, 68.07±0.17 inches; the mean weight, 136.53±1.30 pounds; the mean systolic blood pressure, 117.53±0.86 mm. In a much larger group of freshmen men, who entered the University of Minnesota in 1924, Jackson [2] found a mean age of 20.078± 0.046 years; a mean height of 68.684±0.042 inches; a mean weight of 141.44 ± 0.29 pounds, and a mean systolic blood pressure of 124.28 ± 0.21 mm. A comparison of these figures shows that the two groups were practically identical in age and in height; in weight and in mean systolic blood pressure, however, the mean of the group used in the present study was significantly lower. This might be accounted for, at least in part, by the fact that students who were overweight and

TABLE 1.—*Mean Height of the Several Systolic Readings in Series*

| | Mean | Difference Between Consecutive Readings |
|---|---|---|
| First readings | 118.69 ± 0.69 mm. | |
| | | 3.70 ± 0.95 mm. |
| Second readings | 114.99 ± 0.66 mm. | |
| | | 3.70 ± 0.96 mm. |
| Third readings | 111.29 ± 0.70 mm. | |
| | | 0.43 ± 0.97 mm. |
| Fourth readings | 111.72 ± 0.68 mm. | |
| | | 0.86 ± 0.98 mm. |
| Fifth readings | 110.86 ± 0.71 mm. | |
| | | 0.55 ± 1.01 mm. |
| Sixth readings | 110.31 ± 0.72 mm. | |
| | | 0.82 ± 1.03 mm. |
| Seventh readings | 109.49 ± 0.75 mm. | |
| | | 1.28 ± 1.03 mm. |
| Eighth readings | 108.21 ± 0.73 mm. | |
| | | 0.16 ± 1.02 mm. |
| Ninth readings | 108.37 ± 0.71 mm. | |
| | | 0.47 ± 1.03 mm. |
| Tenth readings | 108.84 ± 0.75 mm. | |
| | | 0.25 ± 1.05 mm. |
| Eleventh readings | 109.19 ± 0.73 mm. | |
| | | 0.31 ± 1.05 mm. |
| Twelfth readings | 109.48 ± 0.76 mm. | |
| All readings | 110.95 ± 0.18 mm. | |

those with definitely elevated blood pressures were not included in the group. From the point of view of normality, it seems that with the lower systolic pressure the group included in this study is even farther from the borderline than was the group included in Jackson's study; certainly, there is no indication that the present group is not well within normal limits.

### MEAN HEIGHT OF THE DIFFERENT READINGS IN THE SERIES

The first computation made was the mean of the systolic pressure of the twelve readings taken on each subject; then the mean of these means for the 100 cases was calculated. This mean which is also the mean

2. Jackson, C. M.: The Physique of Male Students at the University of Minnesota: A Study in Constitutional Anatomy and Physiology, Am. J. Anat. **5**:59 (Sept. 15) 1927.

of all readings taken separately, since the same number of readings was taken in each case, was found to be $110.95 \pm 0.622$ mm.

The means of all the first, second, third, etc., readings., are shown in table 1. The first reading was taken approximately five minutes after the subject sat down at the table, and the subsequent readings at five minute intervals thereafter; so several factors such as rest and allaying apprehension could have contributed to the mean changes in blood pressure that are shown in the table.

The mean of the second readings of the series is $3.70 \pm 0.95$ mm. lower than the mean of the first readings. The actual difference found here is 3.9 times the probable error of the difference; hence, there are approximately 116 chances to 1 that the difference is significant. Between the second and third readings, there is a further decrease of $3.7 \pm 0.96$ mm., a difference also certainly significant. After the third reading, however, the difference between any two consecutive readings is never large enough to be significant; in fact, between most of the consecutive readings, the actual difference is less than the probable error of the difference. The lowest mean in the series of readings is in the eighth, toward which there is a gradual decrease from the fourth and after which there is a slight but progressive increase to the twelfth. Up to the third reading the drop in mean pressure, as already pointed out, is rapid. From the third to the eighth reading the decrease is gradual, but between these two readings the difference is $3.08 \pm 1.01$ mm. This difference indicates that although the variation between any two consecutive readings after the third is not significant, there are approximately 26 chances to 1 that the decrease from the third to the eighth reading is significant. The increase between the minimum eighth and the twelfth is $1.27 \pm 1.05$ mm., a difference certainly not significant.

TABLE 2.—*Highest and Lowest Readings*

| | Highest | Lowest |
|---|---|---|
| First reading | 64 cases | 3 cases |
| Second reading | 12 cases | 2 cases |
| Third reading | 8 cases | 4 cases |
| Fourth reading | 4 cases | 5 cases |
| Fifth reading | 3 cases | 9 cases |
| Sixth reading | 1 case | 8 cases |
| Seventh reading | 2 cases | 12 cases |
| Eighth reading | 3 cases | 21 cases |
| Ninth reading | 0 cases | 14 cases |
| Tenth reading | 2 cases | 6 cases |
| Eleventh reading | 0 cases | 7 cases |
| Twelfth reading | 1 case | 9 cases |

The relative height of the different readings is shown in another manner in table 2. From this it will be seen that in eighty-four of the 100 cases the first, second or third readings were highest, and that in eighty-six of the 100 cases the lowest reading was from the fifth to the twelfth, inclusive.

VARIATION OF BLOOD PRESSURE IN INDIVIDUAL CASES

As a measure of the variation in systolic blood pressure over the twelve readings which were taken on each student, the standard deviation from the mean and the range have been calculated for each case. The distribution of these individual standard deviations, of which the mean is $5.18 \pm 0.162$ mm., is shown in chart 1*A*. Our previous study of variation in blood pressure from day to day [1] showed a mean morning standard deviation of $5.57 \pm 0.167$ mm. and a mean evening standard deviation of $5.86 \pm 0.21$ mm. A comparison of these figures with a mean standard deviation of $5.18 \pm 0.162$ mm. in the present study would

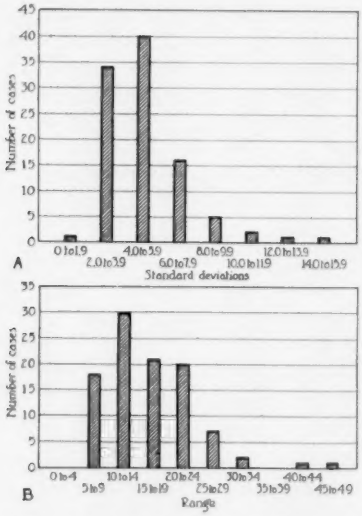


Chart 1.—*A*, distribution chart of the standard deviations of the twelve readings taken in each case from the mean pressure in that case. *B*, distribution chart of the range of systolic blood pressure in the individual cases.

seem to indicate that there is as much variability of blood pressure when the subject rests quietly in a chair as there is in the changing activities from day to day. However, we have noted that there is a significant drop in the mean pressure of the group between the first and second and between the second and third readings of the series. This drop in itself would account for a considerable variability from the mean. Omitting these first two readings and then calculating the mean and the standard deviation from the mean for the last ten readings in each case, we find for the 100 cases a mean of the case means of $109.81 \pm 0.67$ mm. and a mean standard deviation of $3.74 \pm 0.143$ mm. This would indicate that approximately only 28

per cent of the variability is produced by the initial drop in pressure that occurs over the first three readings.

Another measure of variability, which is called the range, is the difference between the lowest and highest readings. From a statistical point of view, range is a much less accurate and satisfactory measure of variation than is standard deviation, because when the range is computed only the extremes are taken into consideration, all intermediate readings being neglected, whether they are bunched or scattered. Nevertheless, range gives some information and is rather generally understood; hence, it was calculated for the cases in this study. The magnitude of these ranges in systolic blood pressure is shown in a distribution chart (1 *B*). The smallest range was 6 mm.; the highest, 46 mm.; the mean, 16.01 ± 0.495 mm.; the mode, 12 mm., and the

TABLE 3.—*The Standard Deviations of the Various Readings in the Series*

| | Standard Deviation from the Mean |
|---|---|
| First readings | 10.28 ± 0.49 mm. |
| Second readings | 9.73 ± 0.76 mm. |
| Third readings | 10.31 ± 0.49 mm. |
| Fourth readings | 10.14 ± 0.48 mm. |
| Fifth readings | 10.54 ± 0.50 mm. |
| Sixth readings | 10.61 ± 0.51 mm. |
| Seventh readings | 11.13 ± 0.53 mm. |
| Eighth readings | 10.77 ± 0.51 mm. |
| Ninth readings | 10.52 ± 0.50 mm. |
| Tenth readings | 11.05 ± 0.52 mm. |
| Eleventh readings | 10.78 ± 0.51 mm. |
| Twelfth readings | 11.22 ± 0.54 mm. |
| All readings | 9.22 ± 0.13 mm. |

median, 15 mm. If the first two readings are omitted, the mean range was 11.97 ± 0.344 mm.

### VARIABILITY OF VARIOUS READINGS IN THE SERIES

For the group as a whole, the relative variability of the different readings of the series as measured by the standard deviation from the mean is shown in table 3. As will be seen from this table, the standard deviation from the mean is practically the same for all of the readings in the series; in fact, between the lowest standard deviation (the second) and the highest (the twelfth) the difference is only 1.49 ± 0.71 mm. In other words, there is only about one chance in five that even this maximum difference is not accidental. Hence, although as pointed out in the previous paragraph, the mean for the successive readings shows a definite downward tendency, there is no significant difference in the reliability of any of the readings of the series.

VARIABILITY AT DIFFERENT LEVELS OF BLOOD PRESSURE

The relation of the mean blood pressures of the group to the variability which these pressures exhibited over the series of twelve readings was calculated by computing the coefficient of correlation between the individual mean pressures and the standard deviations of the twelve readings in each case from the case mean. As this coefficient or correlation was found to be $0.0746 \pm 0.067$, we can say that there is no correlation in this group between the height of the blood pressure and its variability. Table 4 shows the distribution of the data from which the coefficient of correlation was computed. In our previous study of variability of blood pressure,[1] we likewise failed to find any significant correlation between the height of the pressure and its variability. In the present group, however, this lack of any significant correlation is still more surprising because the mean pressure of many of these students was low enough to be rather close to the lower physio-

TABLE 4.—*Distribution Chart of Mean Pressure and Standard Deviation*

| | Standard Deviation | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean Pressure | 1 to 1.9 | 2 to 2.9 | 3 to 3.9 | 4 to 4.9 | 5 to 5.9 | 6 to 6.9 | 7 to 7.9 | 8 to 8.9 | 9 to 9.9 | 10 to 10.9 | 11 to 11.9 | 12 to 12.9 | 13 to 13.9 | 14 to 14.9 | Total |
| 90- 94 | .. | 1 | .. | 2 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 3 |
| 95- 99 | .. | 2 | 1 | .. | 6 | 2 | 1 | .. | .. | .. | .. | .. | .. | .. | 12 |
| 100-104 | .. | 2 | 3 | 6 | 3 | .. | 1 | .. | .. | .. | .. | .. | .. | .. | 15 |
| 105-109 | .. | 2 | 3 | 1 | 5 | 2 | 2 | 1 | .. | .. | .. | 1 | .. | .. | 17 |
| 110-114 | .. | .. | 5 | 4 | 2 | 3 | .. | 1 | .. | 1 | 1 | .. | .. | .. | 17 |
| 115-119 | 1 | 2 | 4 | 2 | 2 | 2 | 1 | 2 | 1 | .. | .. | .. | .. | .. | 17 |
| 120-124 | .. | 1 | 4 | 3 | 2 | 2 | .. | .. | .. | .. | .. | .. | .. | .. | 12 |
| 125-129 | .. | .. | 3 | .. | 2 | .. | .. | .. | .. | .. | .. | .. | .. | .. | 5 |
| 130-134 | .. | .. | 1 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. 1 | 2 |
| Total | 1 | 10 | 24 | 18 | 22 | 11 | 5 | 4 | 1 | 1 | 1 | 1 | 0 | 1 | 100 |

logic limits of blood pressure; in fact, 15 of the 100 cases showed a mean systolic pressure of less than 100.

GRAPHS OF REPRESENTATIVE CASES

In chart 2, twelve consecutive blood pressure readings in eight representative cases are portrayed graphically. In case 1 there is little variation, although a slight tendency for the pressure to increase during the hour. Case 2 shows first a gradual increase in pressure and then a considerable variability, there being a drop of 14 mm. in one five minute interval. Cases 3 and 4 show slight variation with little increase or decrease from the mean. Cases 5, 6 and 7 represent the most frequent type of curve, showing a decided decrease in pressure over the first four or five readings with relatively little variation after that. Case 8 presents a unique curve but is included because it shows first a decrease of 4 mm. followed by a gradual increase of systolic pressure from 118 to 160 mm. in fifty-five minutes. It is interesting to note also that the boy who presented this remarkable sequence of blood pressure

readings was brilliant and highly emotional and was arrested for burglary a few days after the readings were taken.

## COMMENT

In a previous study, the variation in blood pressure in 100 cases from day to day for six consecutive days was found to show in the morning a mean standard deviation of $5.57 \pm 0.167$ mm. and a mean range of $16.29 \pm 0.486$ mm. and in the evening, a mean standard

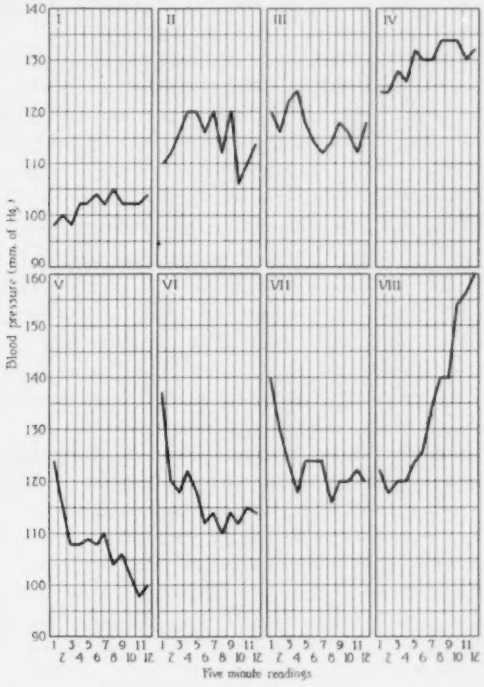


Chart 2.—Graphs of the systolic blood pressure in representative cases with readings taken at five minute intervals.

deviation of $5.86 \pm 0.21$ mm. and a mean range of $17.86 \pm 0.616$ mm. The morning readings were taken between rising and breakfast, and the evening readings just before dinner. Throughout the day the students carried out their usual activities, no attempt being made to control or limit them. In the present study the subjects sat quietly at a table throughout the series of twelve readings, and all readings were taken at approximately the same time in the afternoon. Under these controlled conditions, the mean standard deviation for the twelve readings

was $5.18 \pm 0.162$ mm., and the mean range, $16.01 \pm 0.495$ mm. If the first two readings are omitted from the computations, the mean standard deviation was $3.74 \pm 0.143$ mm. and the mean range, $11.97 \pm 3.44$ mm. The mean pressure for all readings taken on the previous group was $119.76 \pm 0.244$ mm., while the mean pressure for the present group is $110.95 \pm 0.18$ mm. From this it would appear that controlled conditions affect the elevation of blood pressure much more than its variability. A similar conclusion could be drawn from the fact that in the present study there is a decrease in the mean pressure of the successive readings, but no significant changes in their standard deviations.

Although the mean of the 1,200 readings taken on this group was $110.95 \pm 0.18$ mm., the mean systolic pressure of the same students on entrance examinations a few months previously was $117.52 \pm 0.86$ mm. The students naturally were more apprehensive during the entrance examinations than they were during the present study, and at that time only two blood pressure readings were taken on each student. Consequently, the readings on entrance examinations would correspond more closely to the first readings of this series, the mean of which was $118.69 \pm 0.69$ mm. This relationship of the mean pressure in the present study and the mean pressure on entrance examinations bears out the suggestion which was made in a previous paper,[3] that most of the high blood pressure readings that are recorded at the time of the physical examinations performed when the students enter college are due to transient elevations of blood pressure and do not represent a true picture of the usual blood pressure values of the group.

The lowest mean pressure in the series is found in the eighth reading, but no significant difference between successive readings is found after the third reading; furthermore, 84 per cent of the cases showed the highest pressure on the first, second or third readings. From this it would seem that if one takes four blood pressure readings at five minute intervals, there is little probability of obtaining any lower pressure or any less variability even though a considerably greater number of readings is taken.

## SUMMARY

1. Blood pressure readings for 100 healthy men students in the freshman class of the University of Minnesota were taken every five minutes for one hour.

2. The mean systolic pressure of all readings was $110.95 \pm 0.18$ mm.

3. The mean of the standard deviations of the individual cases was $5.18 \pm 0.162$ mm., and the mean range, $16.01 \pm 0.495$ mm.

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3. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures of Young Men, Arch. Int. Med. **36**:151 (Aug.) 1925.

4. The mean of the first three readings of the series shows significant decreases between consecutive readings, but after the third reading the difference between any two consecutive readings is less than the probable error of the difference. There is, however, a gradual decrease in the mean of the series until the eighth reading, which is the lowest point reached. From the eighth to the twelfth reading there is a slight, though not significant, increase in mean pressures.

5. The standard deviations of the various readings of the series show no significant differences, indicating that although in the series of readings the pressure decreases, the variability remains constant.

6. There is no relationship in this series between the level of the systolic pressure and its variability.

# SUGAR TOLERANCE IN ARTHRITIS

## II. ARTHRITIS OF THE MENOPAUSE *

BENJAMIN H. ARCHER, M.D.
NEW YORK

In the previous communication the question of sugar tolerance in chronic infectious arthritis was discussed. In the series of cases reported no evidence was found of a diminished sugar tolerance. Furthermore the results of the study tended to prove that the tolerance for dextrose does not vary with the severity of the arthritic process, and also showed that foci of infection apparently have no specific effect on the sugar storage mechanism.

It is intended, in the present study, to present the data for a parallel series of cases of the menopause type of degenerative arthritis in which the sugar tolerance test was done coincidently with the tests in the aforementioned series of infectious cases. As previously described,[1] the arthritis of the menopause occurs chiefly in obese, middle-aged women at the time of or just after the menopause, and is characterized by the presence of grating knee joints and Heberden's nodes. The evidence at hand points to a noninfectious origin.

As seen in table 1, all of the patients in this series were women. Although the menopause syndrome has been found occasionally in men, associated with signs of endocrine failure, the typical case occurs in women following the climacteric. The average age was 56½ years. The average weight was 172½ pounds (78.2 Kg.), and the average height 5 feet 2½ inches (158.8 cm.). The normal weight for women of this age and height is 141 pounds (64 Kg.). The women in this group were 31½ pounds (14.3 Kg.) overweight. The women in the series of infectious cases were slightly underweight. It is also of interest to note that the average age of women with the arthritis of the menopause is 17 years in advance of the average age of those in the infectious group. These observations are consistent with those made formerly.[2]

The mean systolic blood pressure in this series was 146 mm., and the mean diastolic pressure 81 mm. Six of the patients had a systolic pressure of 150 or more, and five of these had a diastolic pressure of more

* Submitted for publication, Dec. 5, 1928.

* From the Cornell Clinic and the Department of Medicine of Cornell University Medical College.

1. Cecil, R. L., and Archer, B. H.: Arthritis of the Menopause, J. A. M. A. **84**:75 (Jan. 10) 1925.

2. Cecil, R. L., and Archer, B. H.: Classification and Treatment of Chronic Arthritis, J. A. M. A. **87**:741 (Sept. 4) 1926.

than 90. A marked degree of obesity was present in nine cases or in nearly half of the series. In four members of this group, the obesity was associated with hypertension. Practically all of these women had passed the menopause with its concomitant endocrine changes. It has been shown that obesity,[3] hypertension [4] and endocrine dyscrasia [5] may influence the sugar tolerance curve. A study of the foregoing data shows that these factors were operative in this series of cases.

## METHOD

The Hamman and Hirschman [6] method of conducting the test for sugar tolerance was used throughout this study. It consists of the oral administration of 100 Gm. of dextrose while the patient is fasting. Samples of blood and urine are collected one-half, one, two and three hours, respectively, after the ingestion of

TABLE 1.—*Clinical Data on Twenty Cases of Arthritis of the Menopause*

| Number | Name | Age | Weight, Pounds | Height, Inches | Average Weight, Pounds | Blood Pressure | Associated Conditions |
|---|---|---|---|---|---|---|---|
| 1 | H. L. | 51 | 216¾ | 63½ | 141 | 144/ 86 | Obesity |
| 2 | C. W. | 61 | 188½ | 60 | 135 | 180/110 | Obesity, hypertension |
| 3 | G. S. | 59 | 147½ | 68½ | 138 | 126/ 60 | |
| 4 | M. S. | 42 | 151 | 66 | 129 | 110/ 70 | |
| 5 | N. B. | 60 | 151 | 62½ | 139 | 120/ 65 | |
| 6 | J. G. | 49 | 152½ | 66½ | 149 | 170/100 | Hypertension |
| 7 | R. K. | 63 | 185 | 61½ | 135 | 150/ 78 | Obesity |
| 8 | R. S. | 49 | 214½ | 59 | 131 | 140/ 70 | Obesity |
| 9 | A. D. | 52 | 185 | 63 | 141 | 114/ 74 | Obesity |
| 10 | E. T. | 69 | 186 | 65 | 148 | 210/100 | Obesity, hypertension |
| 11 | O. H. | 55 | 150 | 63 | 141 | 146/ 80 | |
| 12 | A. S. | 53 | 132 | 64 | 144 | 130/ 80 | |
| 13 | L. D. | 43 | 169 | 63 | 138 | 120/ 70 | |
| 14 | M. E. | 64 | 189 | 61¼ | 135 | 192/102 | Hypertension, obesity |
| 15 | C. McC. | 60 | 115 | 60½ | 135 | 130/ 60 | |
| 16 | C. C. | 63 | 197 | 62 | 138 | 132/ 72 | Obesity |
| 17 | E. W. | 68 | 178 | 63 | 141 | 146/ 80 | |
| 18 | M. G. | 56 | 142 | 62 | 138 | 140/ 80 | |
| 19 | G. W. | 53 | 168½ | 63¼ | 141 | 140/ 82 | Hypothyroidism |
| 20 | H. R. | 60 | 229½ | 64 | 144 | 174/100 | Obesity, hypertension |

the sugar. The test is preceded by the drawing of the blood during fasting and the collection of a specimen of urine.

The quantitative determination of the blood sugar was made by the Benedict [7] modification of the Lewis and Benedict [8] method. The tests were performed in

3. John, H. J.: The Relationship of Obesity to Carbohydrate Metabolism, Am. J. M. Sc. **173**:184 (Feb.) 1927. Allison, R. S.: Carbohydrate Tolerance in Overweight and Obesity, Lancet **1**:537 (March 12) 1927.

4. O'Hare, J. P.: Glucose Tolerance Test in Chronic Vascular Hypertension, Am. J. M. Sc. **159**:369 (March) 1920. Herrick, W. W.: Hypertension and Hyperglycemia, J. A. M. A. **81**:1942 (Dec. 8) 1923.

5. Janney, N., and Isaacson, J.: The Blood Sugar and Thyroid and Other Endocrine Diseases: The Significance of Hypoglycemia and the Delayed Blood Sugar Curve, Arch. Int. Med. **22**:160 (Aug.) 1918.

6. Hamman, L., and Hirschman, F. L.: Alimentary Hyperglycemia and Glycosuria as a Test for Sugar Tolerance, Arch Int. Med. **20**:761 (Nov.) 1917.

7. Benedict, S. R.: Note on the Determination of Blood Sugar by the Modified Picric Acid Method, J. Biol. Chem. **37**:503, 1919.

8. Lewis, R., and Benedict, S.: A Method for the Estimation of Sugar in Small Quantities of Blood, J. Biol. Chem. **20**:61, 1915.

the Cornell Clinical Pathological Laboratory under the supervision of Dr. Thro. It should be noted that the procedures followed in this series were the same as those employed by Pemberton and Foster,[9] and by me in the study of the infectious cases.

## COMMENT

The results of the tests are shown in table 2.

The mean level during fasting for this series was 0.111 per cent. One-half hour after the administration of the dextrose, the mean reading for the group was 0.166 per cent. At the end of an hour the figure rose to 0.167 per cent. After two hours it was 0.138 per cent, and at the end of three hours the curve dropped to 0.114 per cent. The highest level during fasting in any one case in the series was 0.125 per

TABLE 2.—*Observations on the Blood and Urine*

| | Blood Sugar, in Milligrams per Hundred Cubic Centimeters | | | | | Urine Sugar | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Number | Fasting | ½ Hour | 1 Hour | 2 Hours | 3 Hours | First Test | Second Test | Third Test | Fourth Test | Fifth Test |
| 1 | 125 | 166 | 187 | 136 | ... | Negative | Negative | Negative | Negative | Negative |
| 2 | 100 | 166 | 160 | 115 | 115 | Negative | Negative | Negative | Negative | Negative |
| 3 | 115 | 150 | 136 | 115 | ... | Negative | Negative | ..... | Negative | Negative |
| 4 | 115 | 166 | 150 | 115 | 115 | Negative | Negative | Negative | Negative | Negative |
| 5 | 107 | 150 | 166 | 166 | 136 | Negative | Negative | Negative | Negative | Negative |
| 6 | 115 | 136 | 166 | 125 | 100 | Negative | Negative | Negative | Negative | Negative |
| 7 | 115 | 166 | 200 | 187 | 125 | ..... | Negative | Negative | ..... | Negative |
| 8 | 100 | 166 | 166 | 133 | 100 | Negative | Negative | Negative | Negative | Negative |
| 9 | 125 | 230 | 187 | 166 | ... | Negative | Negative | Negative | Negative | Negative |
| 10 | 100 | 150 | 136 | 136 | 115 | Negative | Negative | Negative | Negative | Negative |
| 11 | 115 | 166 | 166 | 150 | 125 | Negative | Negative | ++ | ++ | ++ |
| 12 | 100 | 150 | 150 | 136 | 115 | Negative | Negative | Negative | Negative | Negative |
| 13 | 115 | 150 | 150 | 150 | ... | Negative | Negative | Negative | ..... | ..... |
| 14 | 115 | 187 | 230 | 187 | 125 | Negative | Negative | Negative | ++ | Negative |
| 15 | 115 | 166 | 187 | 136 | 115 | Negative | Negative | Negative | Negative | Negative |
| 16 | 115 | 187 | 166 | 150 | 100 | ..... | Negative | ++ | ..... | ++ |
| 17 | 125 | 187 | 214 | 136 | 125 | Negative | Negative | Negative | Negative | Negative |
| 18 | 107 | 166 | 150 | 125 | 100 | Negative | Negative | Negative | Negative | Negative |
| 19 | 100 | 136 | 125 | 125 | 115 | Negative | Negative | Negative | Negative | Negative |
| 20 | 90 | 125 | 150 | 107 | 95 | Negative | Negative | Negative | Negative | Negative |

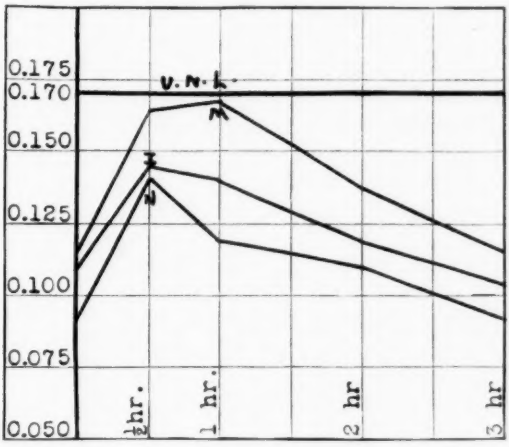
cent. The lowest level was 0.090 per cent. The maximum concentration in any one case after the ingestion of dextrose was 0.23 per cent. The minimum response was 0.136 per cent. Glycosuria was present in only three cases.

Considered by the criteria adopted in the previous study, a postprandial reading of blood sugar of 0.17 per cent or more was taken to be an evidence of a diminished sugar tolerance. As seen in table 2, seven cases, or 35 per cent of the series, fall into this category. The failure of the tolerance curve to return to the fasting level three hours after the administration of dextrose is conceded by practically all observers to be an evidence of a diminished power to assimilate dextrose.

9. Pemberton, R., and Foster, G.: Studies on Arthritis in the Army based on Four Hundred Cases: III. Studies on the Nitrogen, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, Arch. Int. Med. **25**:243 (March) 1920.

Seven, or 35 per cent of the group, had a normal tolerance peak but the curve failed to return to the predextrose level in three hours. Only two cases, or 10 per cent of the series, showed both a maximum concentration of more than 0.17 per cent and a failure of the curve to return to the predextrose level in three hours.

If all cases in which a derangement of the sugar tolerance was present are included, it is found that fourteen cases, or 70 per cent of this series, show a diminished tolerance for dextrose. This result is in marked contrast with the parallel group of infectious cases in which only 15 per cent of the series showed a diminished power to assimilate dextrose. The observations are also abnormal as compared with the




Average curve for the menopause series contrasted with the average curve for the infectious cases, and with the curve for the normal subjects as given by Gray. *N* represents the normal curve; *I*, the curve for the infectious cases; *M*, the curve for the menopause cases, and *U.N.L.*, the upper normal limit as established by Gray.

figures reported by Gray[10] who noted departures from the average tolerance curve in 13 per cent of a series of 300 clinically normal subjects.

In the chart is seen the mean curve of the entire series as contrasted with the mean curves of the series of infectious cases and of Gray's series of 300 normal subjects.

The average predextrose level in the menopause cases (0.111 per cent) was the highest of the three groups. The average blood sugar concentration, one-half hour after the administration of the test load, was 0.163 per cent, a postdextrose rise of 0.052 per cent. After one hour

10. Gray, H.: Blood Sugar Standards, Arch. Int. Med. **31**:241 (Feb.) 1923.

the average maximum concentration (0.167 per cent) was reached. This was a postprandial rise of 0.056 per cent which was above the normal maximum postdextrose rise (0.05 per cent) as determined by Gray. It is interesting to note that the average maximum blood sugar concentration in the menopause group was reached in one hour, while in the infectious cases and in the normal group tested by Gray the greatest concentration was attained in one-half hour. This observation is consistent with that of Spence [11] who found a tendency in older subjects to have a higher and a more prolonged curve. This may be the explanation for the fact that the menopause curve fails to return to the predextrose level in three hours, the average reading at that time being 0.114 per cent, and therefore 0.003 per cent higher than the level maintained during fasting.

A comparison of the sugar tolerance between the menopause and the infectious cases shows that the average maximum blood-sugar concentration in the former group was 0.167 per cent, while in the latter it was only 0.146 per cent. Furthermore, the postdextrose rise in the menopause series was 0.056 per cent while in the infectious group it was only 0.038 per cent. In the infectious cases there was a return to the predextrose level after three hours, while in the menopause series the mean curve at the end of the test was above the level maintained during fasting. Finally, while the average predextrose reading of the menopause cases was only 0.003 per cent higher than the mean predextrose level of the infectious group, three hours after the feeding of dextrose the menopause curve is 0.012 per cent higher than the mean reading for the infectious cases. It is interesting to note that patients with arthritis of the menopause, which is believed by most observers [12] to be of noninfectious origin, show a diminished sugar tolerance while those with arthritis of the chronic infectious type fail to show this deviation from the normal.

There are operative in this series of menopause cases other factors than the disease of the joints which should be given due consideration in the interpretation of the results obtained. It has been shown that obesity, hypertension and endocrine dyscrasia may influence the sugar tolerance curve. As already indicated, five of the patients had a definite hypertension. Three of these, or 60 per cent, showed a diminished tolerance for dextrose. The clinical diagnosis of obesity was made in nine cases of this group. Seven of these, or 78 per cent, showed a lowered sugar tolerance. In four, the obesity was associated with hypertension. Of this group, three, or 75 per cent, showed a diminished

11. Spence, J. C.: Some Observations on Sugar Tolerance, with Special Reference to Variations found at Different Ages, Quart. J. Med. **14**:314 (July) 1921.

12. Symposium on Climacteric Arthritis, Proc. Roy. Soc. Med. **20**:511 (Feb.) 1927.

tolerance for dextrose. While the degree of endocrine disturbance present in this series of patients cannot be accurately determined, it may be assumed that in all of those who are either passing through or have passed the menopause, a definite endocrine dyscrasia is present. To what extent this influences the results obtained, it is impossible to say.

In this series of fourteen patients with arthritis of the menopause who show a diminished sugar tolerance, ten, or 71 per cent, have as associated conditions, hypertension, obesity or both. All fourteen are affected by the endocrine changes of the menopause. As it has been shown that any one of the factors mentioned may cause a diminished tolerance for dextrose, one cannot draw the conclusion that the diminished sugar tolerance found in the present series of cases is due to the chronic disease of the joints that is present.

## CONCLUSIONS

1. In a series of twenty typical cases of arthritis of the menopause fourteen, or 70 per cent, show a diminished sugar tolerance. This is in marked contrast to the parallel series of infectious cases in which only three, or 15 per cent, showed a lowered tolerance for dextrose.

2. Ten of the fourteen cases showing a lowered tolerance for dextrose have, as associated conditions, hypertension or obesity or both.

3. As it has been demonstrated that either hypertension or obesity may cause a lowering of the sugar tolerance, it is impossible to say that the diminished sugar tolerance found in this series of cases is due to the chronic disease of the joints that is present.

# INORGANIC SERUM SULPHATES IN RENAL INSUFFICIENCY

## A COMPARATIVE STUDY OF BLOOD UREA AND CREATININE THE EFFECT OF DIURESIS ON SERUM SULPHATES *

E. G. WAKEFIELD, M.D.
Fellow in Medicine, The Mayo Foundation
ROCHESTER, MINN.

The paucity of knowledge concerning sulphate constituents of the blood probably is due to the fact that methods have not been available which could be used because the quantities of blood required for gravimetric or volumetric procedures were impracticable. During the last few years, however, several so-called microchemical methods have been described. Noteworthy of these methods are the nephlometric method of Denis,[1] the colorimetric method of Hubbard,[2] the gravimetric method of Loeb and Benedict [3] and the volumetric method of White.[4] The latter is a modification of Fiske's [5] volumetric method for determining urinary sulphates.

In recent years several investigators have determined blood sulphates in normal and in various pathologic conditions. Normal sulphate values do not compare very well, as is shown in table 1. One of the factors which might cause disparity of results is that a different method was used in each instance.

Blood sulphates have been as carefully studied in renal disease as in any pathologic condition. In 1921,[6] Denis reported results which indi-

* Submitted for publication, Jan. 9, 1929.

* Work done under supervision of Dr. N. M. Keith, Division of Medicine, The Mayo Clinic.

1. Denis, W.: Sulfates in Blood, J. Biol. Chem. **49**:311, 1921. Denis, W., and Reed, Lucille: Methods for the Determination of Some of the Nonprotein Sulfur Compounds of Blood, J. Biol. Chem. **71**:191, 1926. Denis, W., and Reed, Lucille: A Study of the Influence of Kidney Function on the Concentration of Certain Nonprotein Sulfur Compounds in the Blood, J. Biol. Chem. **73**:41, 1927.

2. Hubbard, R. S.: A Colorimetric Method for the Determination of Sulphate in Serum, J. Biol. Chem. **74**:5, 1927.

3. Loeb, R. F., and Benedict, Ethel M.: Inorganic Sulphates in Human Blood, J. Clin. Investigation **4**:33, 1927.

4. White, H. L.: Studies on Renal Tubule Function: III. Observations on the Excretion of Sulphate with a Modified Technique for the Determination of Inorganic Sulphate in Blood or Plasma, Am. J. Physiol. **65**:537, 1923.

5. Fiske, C. H.: The Determination of Inorganic Sulfate, Total Sulfate, and Total Sulfur in Urine by the Benzidine Method, J. Biol. Chem. **47**:59, 1921.

6. Denis (footnote 1, first reference).

cated that the inorganic sulphates were retained in cases of renal insufficiency, and that this retention had some relation to the retention of nonprotein nitrogen. In 1928, this same observer [7] made a second study in a few cases of nephritis and concluded, "There does not appear to be any direct relation between the retention of nonprotein nitrogen and inorganic sulphate." Loeb and Benedict studied sulphate retention is cardiac and renal disease, and concluded that there was a relationship between retention of sulphate, urea and creatinine.

The objects of the following study were: (1) to determine whether in different types of renal insufficiency inorganic sulphates are retained; (2) if they are retained, to find out whether there is any relationship between this retention and the retention of urea and creatinine, and (3) to study the effect of diuresis on serum sulphates.

TABLE 1.—*Comparisons of Normal Inorganic Sulphates*

| Case | Sulphates in Each 100 Cc. of Plasma (Denis)* | Sulphates in Each 100 Cc. of Serum (Loeb and Benedict) | Sulphates in Each 100 Cc. of Serum (Results by the Author) |
|---|---|---|---|
| 1 | 1.6 | 2.7 | 0.5 |
| 2 | 1.9 | 3.4 | 0.6 |
| 3 | 1.4 | 4.1 | 1.1 |
| 4 | 1.6 | 4.8 | 1.1 |
| 5 | 1.3 | 2.1 | 1.2 |
| 6 | 0.9 | 3.4 | 1.3 |
| 7 | 0.7 | 3.4 | 1.3 |
| 8 | 1.4 | 3.4 | 1.4 |
| 9 | 1.0 | 4.1 | 1.4 |
| 10 | ... | 4.1 | 1.4 |
| 11 | ... | 2.4 | 1.5 |
| 12 | ... | 3.4 | 1.5 |
| 13 | ... | 2.7 | ... |

* Denis' original figures were in terms of sulphur. In this tabulation her figures are expressed in terms of sulphate.

The general types of cases studied may be enumerated as follows: renal insufficiency secondary to generalized vascular disease, 29; acute and chronic diffuse glomerulonephritis, 11; chronic nephrosis, 5; chronic pyelonephritis, 2; renal insufficiency associated with hypertrophy of the prostate, 2; renal lithiasis, 1, and acute renal insufficiency following an operation, 1.

The samples of blood for the determinations were obtained from patients who were in the hospital, and were drawn from two to three hours after the morning meal. In most instances, the patients had been in the hospital for two or more days and were fairly well established on a low protein, low salt diet with a liberal fluid intake of 2,000 cc. or more daily. The blood was allowed to clot, and then the serum was separated by centrifugating. Samples for the determination of urea

7. Denis, W.: Herrmann, G. R., and Reed, Lucille: The Nonprotein Sulphur of the Blood in Certain Pathological Conditions, Arch. Int. Med. **41**:385 (March) 1928.

and creatinine were drawn at the same time as those for the sulphates. Inorganic serum sulphates were determined by a colorimetric method, the principle of which was first described by Hubbard.[8] Creatinine in whole blood was determined by the method of Folin and Wu,[9] and urea by the method of van Slyke and Cullen.[10] All determinations of sulphates were done in duplicate. Normal values for serum sulphate range from 1.5 to 0.5 mg. in each 100 cc. of serum (table 1). It has been observed that values for serum sulphate in patients who are in the hospital for causes other than renal disorders and in whom there is no suspicion of renal disease, are higher than the values shown in table 1. Values for serum sulphate in ten patients who were in the hospital, together with the clinical diagnosis, are given in table 2. This table is offered in the hope that it will illustrate that values for inorganic serum sulphate may be much higher than the normal values given in table 1 without any known reason.

TABLE 2.—*Inorganic Serum Sulphates in Hospitalized Patients Who Did Not Show Evidence of Renal Disease*

| Case | Diagnosis | Inorganic Serum Sulphate in Mg. for Each 100 Cc. |
|---|---|---|
| 1 | Duodenal ulcer | 3.0 |
| 2 | Diabetes mellitus | 3.1 |
| 3 | Diabetes mellitus | 2.2 |
| 4 | Hypoglycemia | 1.9 |
| 5 | Carcinoma stomach | 2.3 |
| 6 | Carcinoma stomach | 2.0 |
| 7 | Pulmonary tuberculosis | 3.0 |
| 8 | Ovarian tumor | 2.5 |
| 9 | Bleeding hemorrhoids, secondary anemia | 2.1 |
| 10 | Neurasthenia | 2.5 |

For the sake of clearness, the results are divided into three arbitrary groups. The results recorded in table 3 were obtained in cases in which the urea content of the whole blood was more than 100 mg. in each 100 cc.; in table 4, in cases in which the urea content of the whole blood was from 70 to 100 mg. in each 100 cc.; in table 5, in the cases in which the urea content of the whole blood was from 40 to 70 mg. in each 100 cc.

The patients who made up group 1 (table 3) were in the terminal stages of different types of renal and vascular disease. Case 14, in which the highest sulphate value was found, was an instance of the

8. Full details of the author's experience with this method are included in Wakefield, E. G.: The Calorimetric Determination of Total and Inorganic Sulphates in Blood Serum, Urine and Other Body Fluids, J. Biol. Chem. **81**:713 (March) 1929.

9. Folin, Otto; and Wu, Hsien: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

10. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urase and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914.

so-called malignant hypertension of Keith and Wagener.[11] Renal insufficiency developed, and the patient died from uremia. It is well to point out the fact that the values for inorganic sulphates in this group probably are technically a little high as the phosphates were not removed from the trichloracetic acid filtrate. The important thing is that without a single exception, inorganic sulphates are increased. There is no strict correlation between the increase of sulphates and retention

TABLE 3.—*Comparison of Retention of Urea and Creatinine with the Quantity of Inorganic Serum Sulphates in Uremia*

| Case. | Urea, Mg. in Each 100 Cc. of Whole Blood | Creatinine, Mg. in Each 100 Cc. of Whole Blood | Inorganic Sulphate, Mg. Sulphate in Each 100 Cc. of Blood Serum |
|---|---|---|---|
| 1 | 106 | 4.1 | 9.8 |
| 2 | 113 | 6.8 | 8.1 |
| 3 | 116 | 5.7 | 8.2 |
| 4 | 117 | 6.5 | 6.5 |
| 5 | 125 | 5.0 | 8.4 |
| 6 | 127 | 5.0 | 7.2 |
| 7 | 128 | 7.0 | 5.0 |
| 8 | 155 | 7.6 | 11.6 |
| 9 | 163 | 8.0 | 12.0 |
| 10 | 209 | 3.7 | 35.8 |
| 11 | 212 | 9.0 | 18.0 |
| 12 | 256 | 11.2 | 23.2 |
| 13 | 258 | 11.4 | 15.0 |
| 14 | 263 | 4.7 | 36.2 |
| 15 | 274 | 12.2 | 29.8 |
| 16 | 328 | 11.0 | 29.0 |

TABLE 4.—*Comparison of Retention of Urea and Creatinine with the Quantity of Inorganic Serum Sulphates in Cases in Which the Values for Blood Urea Were Between 70 and 100 mg. in Each 100 cc.*

| Case | Urea, Mg. in Each 100 Cc. of Whole Blood | Creatinine, Mg. in Each 100 Cc. of Whole Blood | Inorganic Sulphates, Mg. Sulphate in Each 100 Cc. of Blood Serum |
|---|---|---|---|
| 1 | 70 | 2.4 | 4.3 |
| 2 | 71 | 2.6 | 9.8 |
| 3 | 74 | 2.7 | 3.7 |
| 4 | 77 | 3.3 | 9.8 |
| 5 | 78 | 3.5 | 4.7 |
| 6 | 83 | 3.5 | 3.8 |
| 7 | 89 | 5.2 | 8.2 |
| 8 | 90 | 4.5 | 6.8 |
| 9 | 93 | 3.5 | 7.5 |
| 10 | 98 | 5.8 | 8.1 |

of urea and of creatinine. For example, one might point out the fact that the value of serum sulphate in case 10 is practically twice that in case 11, whereas there is a difference of 3 mg. in each 100 cc. in the values of blood urea in the same two cases. On comparison of the

11. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Jan.) 1928. Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, ibid. **34**:374 (Sept.) 1924.

values of creatinine in these two cases, it is seen that the reverse is true; that is, in case 11 twice as much creatinine is retained as in case 10.

In group 2 (table 4) there is wider variation in the results. The highest values for sulphate are in cases 2 and 4, between which there is a difference of 6 mg. of urea in each 100 cc. of blood. It happens that the first and last cases have the lowest and the highest values for urea and creatinine, respectively, but between cases 9 and 10 there is a difference of 2.3 mg. in the blood creatinine in each 100 cc., with a difference of only 5 mg. in the blood urea in each 100 cc. and a difference of 0.6 mg. in each 100 cc. in the values for serum sulphate.

The values for inorganic sulphates in group 3 (table 5) vary more than in either of the other two groups. Practically the same can be

TABLE 5.—*Comparison of Retention of Urea and Creatinine with Quantity of Inorganic Serum Sulphates in Cases in Which the Values for Blood Urea Were Between 40 and 70 mg. in Each 100 cc.*

| Case | Urea, Mg. in Each 100 Cc. of Whole Blood | Creatinine, Mg. in Each 100 Cc. of Whole Blood | Inorganic Sulphates, Mg. Sulphate in Each 100 Cc. of Blood Serum |
|---|---|---|---|
| 1 | 40 | 1.6 | 2.0 |
| 2 | 41 | 2.0 | 2.6 |
| 3 | 48 | 2.9 | 6.4 |
| 4 | 49 | 1.4 | 3.2 |
| 5 | 50 | 2.0 | 2.5 |
| 6 | 54 | 2.1 | 2.7 |
| 7 | 60 | 2.7 | 4.0 |
| 8 | 62 | 4.5 | 4.8 |
| 9 | 63 | 2.3 | 5.9 |
| 10 | 64 | 3.2 | 3.8 |

said of the creatinine. In case 1 in this group the values for urea and creatinine are normal, while there is retention of sulphates. With a difference of 1 mg. in each 100 cc. of blood, there is practically twice as much creatinine in each 100 cc. of blood in case 8 as in case 9.

In all the determinations, the values for inorganic serum sulphates are relatively higher than for the creatinine. There are wide variations, but the significant thing is that when there is a definite retention of either urea or creatinine, or an increase in sulphates, there is usually retention or increase of the other two. There are exceptions to this, an example of which is case 1, table 5. It may be that variations in renal lesions account for some of the variations observed in the relative degree of retention of urea, creatinine and sulphates. This does not explain the possibilities for the wide variations in values for inorganic serum sulphates. Attempts have been made to ascertain some of the conditions which influence the level of inorganic serum sulphates. Following Denis' suggestion that diuresis may influence the level of serum sulphates, the following experiments were carried out.

In five cases of edema of renal origin in which merbaphen was given intravenously in doses of 2 cc., inorganic serum sulphates were determined just before and six hours after the administration of the drug, with the results shown in table 6. It is seen that in every case there is a small but a definite decrease in the sulphates after diuresis.

In another set of experiments designed to test the influence of the intake and output of fluid on inorganic serum sulphates, patients with suspected renal disease were given the water and concentration tests of Volhard and Fahr, in the order named. On the morning of the day for

TABLE 6.—*Comparison of Inorganic Serum Sulphates Before and After Intravenous Administration of 2 cc. of Merbaphen* *

| Case | Sulphates Before Merbaphen, Mg. Sulphate in Each 100 Cc. of Serum | Sulphate Six Hours After Merbaphen, Mg. Sulphate in Each 100 Cc. of Serum | Amount of Urine Voided During the Six-Hour Period After Merbaphen, Cc. |
|---|---|---|---|
| 1 | 2.5 | 2.3 | 1,800 |
| 2 | 3.0 | 2.9 | 1,500 |
| 3 | 2.3 | 2.0 | 1,200 |
| 4 | 3.2 | 2.5 | 1,750 |
| 5 | 2.3 | 1.3 | 1,000 |

* Patients received a carefully weighed diet, with daily fluids less than 1,000 cc.

TABLE 7.—*Comparison of Inorganic Serum Sulphates Before and After the So-Called Water and Concentration Tests of Volhard and Fahr*

| Case | Before 1,500 Cc. of Water by Mouth | Four Hours After 1,500 Cc. of Water by Mouth | Thirty Hours Without Water Except the 200 Cc. in the Diet |
|---|---|---|---|
| 1 | 1.3 | 0.7 | 0.9 |
| 2 | 1.6 | 1.6 | 1.5 |
| 3 | 1.5 | 1.4 | 2.1 |
| 4 | 2.2 | 2.3 | 2.1 |
| 5 | 1.9 | 2.2 | 2.1 |
| 6 | 9.8 | 8.5 | 10.9 |
| 7 | 6.8 | 7.1 | 7.9 |
| 8 | 1.5 | 1.4 | 1.7 |
| 9 | 1.2 | 1.1 | 1.5 |
| 10 | 1.8 | 1.2 | 2.0 |

the water test, before the water was given, blood was taken for the determination of sulphates. Breakfast was omitted, and 1,500 cc. of water was given at 8 a. m. At noon, after the diuresis caused by the intake of water, another sample of blood was taken for determination of sulphates. The changes after diuresis caused by intake of water were not significant. A day intervened between the water and the concentration tests, during which the patient was allowed a liberal intake of fluid and a low protein diet. After the patient had been receiving the "concentration diet" for about thirty hours, during which time the water in the foods of this diet was all the patient had, blood was taken for determination of sulphates. The results are shown in table 7. The

evidence of renal insufficiency in cases 6 and 7 are tabulated in table 8; in this group, in cases 6 and 7 there was definite renal insufficiency. It is interesting to note that only in these two cases was there a definite increase in sulphates while the patients were undergoing the concentration test. This is pointed out here because it may be significant and, too, this observation is in accord with some data I have on inorganic serum sulphates in Addison's disease.

Apropos of the effect of diuresis on serum sulphates, two patients with diabetes insipidus were studied. Both of the patients were men

TABLE 8.—*Evidence for a Diagnosis of Renal Insufficiency in Cases 6 and 7 in Table 7*

| Case | Urine Analysis | | Hemoglobin (Dare) per Cent | Phenolsulphonphthalein Recovered at the End of Two Hours | Blood Urea, Mg. in Each 100 Cc. | Blood Creatinine, Mg. in Each 100 Cc. | Lowest Specific Gravity on Water Test | Highest Specific Gravity on Concentration Test | Blood Pressure, Mm. of Hg | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Systolic | Diastolic |
| 6 | Hyaline casts..... | ++ | 60 | 15% | 85 | 3.3 | 1.004 | 1.014 | 180 | 100 |
| | Granular casts.... | ++ | | | | | | | | |
| | Red blood cells.... | ++ | | | | | | | | |
| | Pus..... | +++ | | | | | | | | |
| 7 | Hyaline casts..... | +++ | 40 | 20% | 74 | 2.4 | 1.005 | 1.015 | 130 | 85 |
| | Granular casts.... | ++ | | | | | | | | |
| | Red blood cells.... | +++ | | | | | | | | |
| | Pus..... | + | | | | | | | | |

TABLE 9.—*Inorganic Serum Sulphates in Chronic Nephrosis*

| Case | Sulphates, Mg. in Each 100 Cc. of Serum |
|---|---|
| 1 | 1.8 |
| 2 | 3.0 |
| 3 | 1.4 |
| 4 | 1.5 |
| 5 | 2.0 |

and were voiding more than 4,000 cc. of urine daily. Determinations on one of them showed 0.5 and on the other, 0.4 mg. of sulphate in each 100 cc. of serum. The quantity of sulphates in the serum of these patients was of a low normal value. Diuresis, of course, influences the level of serum sulphates, but in these two cases prolonged diuresis had failed to do more than lower the sulphates to low normal values.

Five cases of nephrosis in which blood urea and creatinine were normal were studied, with the results shown in table 9. The values for inorganic serum sulphates in these five cases of nephrosis are, on an average, higher than the average normal values given in table 1. But the values in table 9 are not higher than values obtained on patients hospitalized for causes other than renal disease, as shown in table 2.

SUMMARY

In cases of renal insufficiency, when the blood urea is above 100 mg. in each 100 cc., values for inorganic serum sulphate are high.

With blood urea values between 70 to 100 mg. in each 100 cc., serum sulphate concentration usually is increased. However, this increase in serum sulphates apparently has no direct correlation with blood urea and creatinine concentrations.

Some evidence is offered that diuresis lowers the inorganic serum sulphates.

Determination of inorganic serum sulphates in the five cases of chronic nephrosis studied were approximately normal. This would indicate that there may not be any retention of inorganic sulphate in nephrosis.

Attention is called to the fact that patients who do not show evidence of renal disease may have higher inorganic serum values for sulphate than those observed in normal active persons.

# A CHEMICAL STUDY OF URINE AS EFFECTED BY COMBINATIONS OF AMMONIUM CHLORIDE AND ·METHENAMINE *

EDWIN C. WISE, M.S.
AND
FREDERICK W. HEYL, PH.D.
KALAMAZOO, MICH.

Since the classic paper of Hanzlik and Collins,[1] the use of methenamine has been greatly restricted, and it finds its chief application as a urinary antiseptic in acid urines. In this work acid sodium phosphate is suggested as an acidifying agent, and this suggestion is now found in most textbooks. Since that time ammonium chloride has been recommended for the same purpose, and Helmholz [2] reported favorably on the combined use of methenamine and ammonium chloride in pyelitis in children.

Trendelenburg [3] reported the dissociation curve of methenamine at increasing degrees of acidity. At a $p_H$ of 5.2 and at a temperature of 38 C., about 8 per cent of the drug is hydrolyzed in six hours. In two hours considerably less than this, approximately 3.4 per cent will be converted into formaldehyde. At a $p_H$ of 6.3, about 1 per cent is hydrolyzed in two hours. In six hours he found only 1.5 per cent.

In the urine, one may hope to approach a $p_H$ of 5.2 ($\pm 0.2$). Assuming that 8 per cent were hydrolyzed, a dose of 100 grains (6 Gm.) would throw about 0.5 Gm. of formaldehyde into approximately 2,000 cc. of urine, making a concentration of 1 : 4,000. If the $p_H$ is 6.3 per cent, the maximum calculated concentration would be about 1 : 20,000. In no case would these maximum values be obtained, nor would uniform concentrations of formaldehyde result in tests on different patients nor in tests made during different periods of the day on the same patient. Falk and Sugiura [4] showed that the concentration of methenamine recovered in the urine varied from 45 to 92 per cent when the drug is taken in doses of 15 grains (0.97 Gm.). It is therefore evident that the difference between futile and effective urinary antisepsis

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* From the Research Laboratories, The Upjohn Company.

1. Hanzlik, P. J., and Collins, R. J.: Hexamethylenamin: The Liberation of Formaldehyde and the Antiseptic Efficiency under Different Chemical and Biological Conditions, Arch. Int. Med. **12**:578 (Nov.) 1913.

2. Helmholz, H. F.: Therapeutic Value of Hexylresorcinol in Chronic Pyelitis of Childhood, Am. J. Dis. Child. **32**:396 (Sept.) 1926.

3. Trendelenburg, Paul: Biochem. Ztschr. **95**:146, 1919.

4. Falk, K. G., and Sugiura, K.: J. Pharmacol. & Exper. Therap. **8**:39, 1915.

can be explained readily on the basis of known factors; furthermore, the effect of the drug is easily lost.

The question of proper dosage of each of the factors is therefore important, and all results not obtained on a standard basal diet are of little help as the diet itself without a doubt frequently offsets the effectiveness of the urinary acidifier. If the diet contains milk, the high buffer action of the inorganic salts will without a doubt offset the effectiveness of acid sodium phosphate in this direction. As a matter of fact, the common use of this acidifier requires dietary directions at the same time, for Henderson and Palmer [5] showed that its acidifying effect was mild, and Hanzlik and Collins [1] gave it in purgative doses to secure a desirable liberation of formaldehyde.

## EXPERIMENTAL CONDITIONS

To secure further information we varied the time and dosage of methenamine and ammonium chloride over a considerable range, to find out what quantities would prove sufficient on a basal diet which gave a bland neutral urine. The conditions of the experiments were as follows:

*Diet.*—It was desired to select a basal diet that would allow plenty of food, be nearly normal, easily reproducible and give the urine a $p_H$ of from 6.5 to 7 so as to make changes in acidity definitely marked. The following diet was satisfactory in these respects:

White bread, 250 Gm.
Boiled potatoes, 300 Gm.
Canned tomatoes, 150 Gm.
Canned peaches, 250 Gm.
Bananas, 150 Gm.
Canned asparagus, 100 Gm.
Butter, 90 Gm.
Milk, 1 pint
Cream, ½ pint
Water as desired

*Subjects.*—The subjects for the experiment were normal young men employed around the plant by day at light labor. They were restricted in no way except as to food and drink.

*Samples.*—Samples of urine were collected in most cases at intervals of two hours from 8 a. m. until 10 p. m. The next sample was collected at 6 a. m. and together with those previously collected made up the twenty-four hour sample. The samples were all preserved under toluene. The various determinations were made as soon as the samples were voided.

5. Henderson, L. J., and Palmer, W. W.: J. Biol. Chem. **14**:81, 1913.

*Methenamine.*—Methenamine was qualitatively determined by the bromine water test. A few drops of bromine water added to the urine gave an abundant orange precipitate in the presence of methenamine.

*Titratable Acidity.*—A 10 cc. sample of urine was titrated in the usual manner with tenth-normal alkali and phenolphthalein. The result was expressed as cubic centimeters of tenth-normal sodium hydroxide per hundred cubic centimeters of urine.

*Hydrogen Ion Concentration.*—The hydrogen ion concentration was determined electrometrically by the use of a Leeds and Northrup potentiometer and a quinhydrone electrode.

*Formaldehyde.*—The amount of formaldehyde was estimated by a modification of the phlorglucin colorimetric method of Hanzlik and Collins.[1] Congo-red solutions were prepared and standardized against solutions of formaldehyde of known concentration. Smaller volumes were used than in the original method of Hanzlik.

*Plan of Experiment.*—The basal diet was fed for two or three days until the average twenty-four hour $p_H$ was fairly constant and approximately 6.5. Considerable experience with the diet on numerous subjects showed that the urinary $p_H$ would be approximately 6.5 when the diet was fed until the $p_H$ of the urine remained practically constant. When this point of equilibrium was reached (usually in from two to three days), the substances to be tried were given, dissolved in water.

## EXPERIMENTS

EXPERIMENT 1.—Two subjects, W. B. and F. D., were fed the basal diet for two days, and during the next three days were fed in addition five doses daily of a mixture of ammonium chloride, 15 grains (0.97 Gm.), and methenamine, 7½ grains (0.49 Gm.), making 75 grains (4.87 Gm.) of ammonium chloride and 37½ grains (2.43 Gm.) of methenamine per day. The doses were given at 9 a.m., 11 : 30 a.m., 2 p.m., 4 : 30 and 7 p.m. Each dose was taken in approximately from 6 to 8 ounces of water. Samples of urine were collected at 8 a. m., 10, 12 noon, 2 p.m., 4, 6, 8 and 10 p.m. The amount of formaldehyde, H-ion concentration, titratable acidity, methenamine and volume were determined as soon as the samples were voided. The remainder of the samples were combined, preserved under toluene, and after the complete twenty-four hour output was obtained the H-ion concentration and acidity were determined on this composite sample. The data for this sample are listed as "twenty-four hour average" in the accompanying tables. The subjects were fed at 8 a.m., 12 noon and 5 p.m. The data are shown in table 1 and are illustrated in chart 1.

In table 1, it is shown clearly that while the urinary acidity of the subject is controlled desirably at points where hydrolysis can be expected, nevertheless, the dosage of methenamine is rather low, since the concentration of formaldehyde approximates 1 : 35,000. The early morning urine shows uniformly a concentration of 1 : 40,000, and dur-

TABLE 1.—*Results of Experiment 1*

| Time | Volume | Titratable Acidity | $p_H$ | Remarks | Volume | Titratable Acidity | $p_H$ | Formaldehyde | Methenamine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| **Subject 1** | | **First Day** | | | | | **Third Day** | | | |
| 10 a.m. | 165 | 34.0 | 5.72 | Basal diet | 195 | 7.0 | 6.44 | None | + | Five doses of |
| 12 m. | 530 | 2.2 | 6.86 | period | 115 | 31.0 | 5.68 | 1:60,000 | + | methenamine, |
| 2 p.m. | 220 | 7.5 | 6.84 | | 280 | 25.0 | 5.52 | 1:50,000 | + | 7½ grains, |
| 4 p.m. | 430 | 4.5 | 6.48 | Two days | 130 | 56.0 | 5.38 | 1:50,000 | + | ammonium |
| 6 p.m. | 270 | 7.0 | 6.48 | | 165 | 48.5 | 5.51 | 1:30,000 | + | chloride, 15 |
| 8 p.m. | 370 | 4.5 | 7.14 | | 345 | 11.5 | 6.02 | 1:100,000 | + | grains at 9, |
| 10 p.m. | 135 | 1.5 | 7.40 | | 140 | 34.0 | 5.96 | 1:60,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 400 | 14.5 | 6.42 | End of first day | 330 | 40.0 | 5.72 | 1:40,000 | + | End of third day |
| 24 hour average | 2,520 | 7.0 | 6.81 | | 1,700 | 27.0 | 5.80 | ..... | + | |
| | | **Second Day** | | | | | **Fourth Day** | | | |
| 8 a.m. | ... | .... | .... | | 115 | 34.0 | 5.80 | 1:60,000 | + | |
| 10 a.m. | 70 | 23.0 | 6.22 | | 130 | 25.0 | 5.66 | 1:100,000 | + | |
| 12 m. | 80 | 13.0 | 6.46 | | 220 | 25.5 | 5.42 | 1:50,000 | + | Same dose |
| 2 p.m. | 235 | 8.0 | 6.60 | | 420 | 18.0 | 5.36 | 1:40,000 | + | |
| 4 p.m. | 100 | 21.0 | 6.10 | | 165 | 55.0 | 5.29 | 1:30,000 | + | |
| 6 p.m. | 155 | 14.0 | 6.44 | | 165 | 54.0 | 5.34 | 1:25,000 | + | |
| 8 p.m. | 320 | 3.5 | 7.12 | | 205 | 24.5 | 5.41 | 1:40,000 | + | |
| 10 p.m. | 145 | 3.0 | 7.60 | | 145 | 41.5 | 5.52 | 1:50,000 | + | |
| 6 a.m. | 470 | 14.0 | 6.72 | End of second day | 355 | 41.5 | 5.65 | 1:40,000 | + | End of fourth day |
| 24 hour average | 1,575 | 8.5 | 6.91 | | 1,920 | 32.0 | 5.51 | | | |
| | | | | | **Fifth Day** | | | | | |
| 8 a.m. | ... | .... | .... | | 100 | 40.0 | 5.76 | 1:80,000 | + | |
| 10 a.m. | ... | .... | .... | | 105 | 36.5 | 5.56 | 1:100,000 | + | |
| 12 m. | ... | .... | .... | | 220 | 22.5 | 5.48 | 1:50,000 | + | |
| 2 p.m. | ... | .... | .... | | 345 | 19.0 | 5.48 | 1:50,000 | + | Same dose |
| 4 p.m. | ... | .... | .... | | 270 | 29.0 | 5.50 | 1:45,000 | + | |
| 6 p.m. | ... | .... | .... | | 175 | 48.5 | 5.31 | 1:35,000 | + | |
| 8 p.m. | ... | .... | .... | | 330 | 22.0 | 5.44 | 1:40,000 | + | |
| 10 p.m. | ... | .... | .... | | 185 | 34.0 | 5.48 | 1:35,000 | + | |
| 6 a.m. | ... | .... | .... | | 420 | 34.5 | 5.68 | 1:40,000 | + | End of fifth day |
| 24 hour average | ... | .... | .... | | 2,150 | 29.0 | 5.66 | ..... | + | |
| **Subject 2** | | **First Day** | | | | | **Third Day** | | | |
| 10 a.m. | 340 | 12.5 | 6.58 | Basal diet | 135 | 16.0 | 6.08 | ..... | + | Five doses of |
| 12 m. | 135 | 14.5 | 6.68 | | 90 | 46.5 | 5.41 | 1:50,000 | + | methenamine, |
| 2 p.m. | 220 | 8.0 | 6.88 | | 410 | 18.0 | 5.46 | 1:50,000 | + | 7½ grains, |
| 4 p.m. | 155 | 9.0 | 7.14 | | 165 | 51.5 | 5.30 | 1:30,000 | + | ammonium |
| 6 p.m. | 180 | 12.0 | 7.12 | | 80 | 84.5 | 5.42 | 1:25,000 | + | chloride, 15 |
| 8 p.m. | 520 | 3.5 | 7.20 | | 115 | 58.5 | 5.36 | 1:50,000 | + | grains at 9, |
| 10 p.m. | 90 | 9.0 | 7.44 | | 90 | 65.5 | 5.64 | 1:35,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 520 | 23.0 | 6.26 | End of first day | 650 | 29.5 | 5.72 | 1:40,000 | + | |
| 24 hour average | 2,150 | 9.5 | 6.78 | | 1,735 | 32.0 | 5.66 | | | |
| | | **Second Day** | | | | | **Fourth Day** | | | |
| 8 a.m. | ... | .... | .... | | 70 | 33.0 | 5.36 | 1:90,000 | + | |
| 10 a.m. | 115 | 6.5 | 7.00 | Basal diet | 120 | 28.5 | 5.24 | 1:100,000 | + | Same dose |
| 12 m. | 80 | 17.5 | 6.54 | | 110 | 50.5 | 5.28 | 1:50,000 | + | |
| 2 p.m. | 100 | 29.0 | 6.44 | | 280 | 37.5 | 5.12 | 1:30,000 | + | |
| 4 p.m. | 120 | 16.0 | 6.84 | | 205 | 51.0 | 5.24 | 1:25,000 | + | |
| 6 p.m. | 170 | 14.0 | 6.84 | | 110 | 88.0 | 5.36 | 1:30,000 | + | |
| 8 p.m. | 260 | 7.0 | 6.68 | | 210 | 40.5 | 5.24 | 1:30,000 | + | |
| 10 p.m. | 105 | 7.5 | 7.36 | | 390 | 22.0 | 5.64 | 1:50,000 | + | |
| 6 a.m. | 530 | 19.5 | 6.18 | End of second day | 605 | 36.5 | 5.68 | 1:40,000 | + | |
| 24 hours average | 1,480 | 14.5 | 6.66 | | 2,010 | 37.5 | 5.50 | ..... | + | |
| | | | | | **Fifth Day** | | | | | |
| 8 a.m. | ... | .... | .... | | 90 | 31.0 | 5.41 | 1:100,000 | + | |
| 10 a.m. | ... | .... | .... | | 215 | 18.0 | 5.07 | 1:100,000 | + | |
| 12 m. | ... | .... | .... | | 200 | 34.0 | 5.16 | 1:40,000 | + | Same dose |
| 2 p.m. | ... | .... | .... | | 375 | 28.5 | 5.16 | 1:30,000 | + | |
| 4 p.m. | ... | .... | .... | | 385 | 24.5 | 5.24 | 1:30,000 | + | |
| 6 p.m. | ... | .... | .... | | 140 | 52.0 | 5.40 | 1:35,000 | + | |
| 8 p.m. | ... | .... | .... | | 345 | 24.5 | 5.27 | 1:40,000 | + | |
| 10 p.m. | ... | .... | .... | | 245 | 22.0 | 5.50 | 1:45,000 | + | |
| 6 a.m. | ... | .... | .... | | 520 | 38.5 | 5.56 | 1:35,000 | + | |
| 24 hours average | ... | .... | .... | | 2,715 | 27.5 | 5.48 | ..... | + | |

ing the early hours of the day about four hours are required to bring the urinary concentration again up toward the maximum.

EXPERIMENT 2.—This experiment was carried out exactly as experiment 1, except that the two subjects, W.B. and F.D., were given a larger dose of methenamine. They received 15 grains each of ammonium chloride and methenamine at regular intervals, avoiding meals as far as possible. For two days five doses were given and on the last day seven doses. A third subject, E.G., was kept on the original dosage.

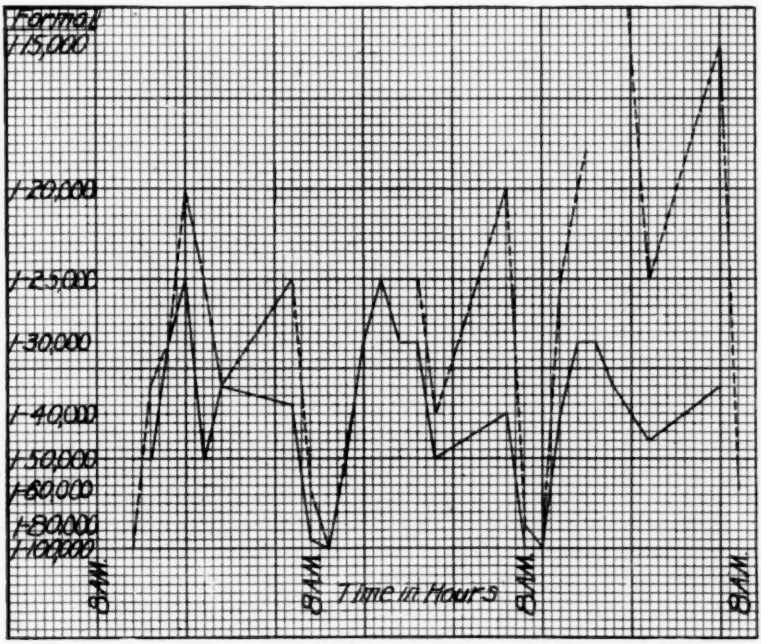


Chart 1.—Difference in effectiveness of 15 over 7½ grains of methenamine with 15 grains of ammonium chloride. The broken line represents the results from 75 grains; the solid line, from 37½ grains.

For the days on which 75 grains of methenamine was given, it will be observed that (although the urinary acidity is approximately the same as in experiment 1) the concentration of formaldehyde is of a somewhat higher order, approximately 1:30,000. Particularly the early morning urine showed a much higher concentration of about 1:20,000.

In general, it must be admitted that so far as the urinary concentration of formaldehyde in the day-time urine was concerned, at the same $p_H$ there was but little increase due to the additional methenamine. We therefore extended the experiment on the third day to seven doses,

TABLE 2.—*Results of Experiment 2*

| Time | Volume | Titratable Acidity | $p_H$ | Remarks | Volume | Titratable Acidity | $p_H$ | Formaldehyde | Methenamine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject 1 | First Day | | | | Third Day | | | | | |
| 10 a.m. | 95 | 72.5 | 5.60 | | 120 | 22.0 | 6.54 | ..... | + | Five doses of |
| 12 m. | 470 | 3.5 | 6.54 | | 495 | 6.0 | 6.28 | +1:100,000 | + | methenamine, |
| 2 p.m. | 370 | 4.5 | 6.27 | | 355 | 17.0 | 5.74 | 1:30,000 | + | 15 grains, |
| 4 p.m. | 125 | 30.5 | 5.66 | | 140 | 52.0 | 5.63 | 1:30,000 | + | ammonium |
| 6 p.m. | 95 | 29.0 | 6.27 | | 195 | 35.5 | 5.63 | 1:25,000 | + | chloride, 15 |
| 8 p.m. | 220 | 8.0 | 6.83 | | 130 | 31.0 | 5.72 | 1:35,000 | + | grains, at 9, |
| 10 p.m. | 170 | 4.0 | 7.58 | | 110 | 53.5 | 5.74 | 1:50,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 345 | 21.5 | 6.46 | | 330 | 35.0 | 5.81 | 1:25,000 | + | |
| 24 hour average | 1,890 | 11.0 | 6.49 | | 1,875 | 22.0 | 5.84 | ..... | + | |
| | Second Day | | | | Fourth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 90 | 37.0 | 5.65 | 1:50,000 | + | |
| 10 a.m. | 130 | 34.5 | 6.13 | | 240 | 16.5 | 5.74 | 1:100,000 | + | |
| 12 m. | 420 | 5.0 | 6.50 | | 330 | 17.0 | 5.66 | 1:50,000 | + | |
| 2 p.m. | 275 | 9.0 | 6.81 | | 440 | 16.0 | 5.65 | 1:35,000 | + | Same dose |
| 4 p.m. | 100 | 18.0 | 6.62 | | 155 | 52.5 | 5.54 | 1:25,000 | + | |
| 6 p.m. | 110 | 24.0 | 6.42 | | 340 | 25.5 | 5.55 | 1:30,000 | + | |
| 8 p.m. | 240 | 5.0 | 7.22 | | 400 | 17.5 | 5.75 | 1:40,000 | + | |
| 10 p.m. | 170 | 3.0 | 7.55 | | 345 | 14.5 | 5.92 | 1:50,000 | + | |
| 6 a.m. | 470 | 14.0 | 6.68 | | 255 | 54.5 | 5.60 | 1:20,000 | + | |
| 24 hour average | 1,915 | 9.0 | 6.80 | | 2,595 | 21.0 | 5.65 | ..... | .. | |
| | | | | | Fifth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 75 | 39.0 | 5.76 | 1:50,000 | + | Seven doses of |
| 10 a.m. | ... | .... | .... | | 155 | 24.0 | 5.54 | 1:60,000 | + | same sub- |
| 12 m. | ... | .... | .... | | 210 | 32.5 | 5.48 | 1:25,000 | + | stances at |
| 2 p.m. | ... | .... | .... | | 530 | 15.5 | 5.33 | 1:25,000 | + | 8:30, 10, 11:30, |
| 4 p.m. | ... | .... | .... | | 75 | 63.5 | 5.30 | 1:20,000 | + | 1, 3, 7, 9 |
| 6 p.m. | ... | .... | .... | | 120 | 56.5 | 5.31 | 1:10,000 | + | |
| 8 p.m. | ... | .... | .... | | 300 | 21.0 | 5.88 | 1:35,000 | + | |
| 10 p.m. | ... | .... | .. | | 170 | 34.5 | 5.76 | 1:25,000 | + | |
| 6 a.m. | ... | .... | .... | | 145 | 41.5 | 5.56 | 1:25,000 | + | |
| 24 hours | ... | .... | .... | | 1,780 | 25.0 | 5.65 | ..... | + | |
| 8 a.m. | ... | .... | .... | | 70 | 44.0 | 5.51 | 1:40,000 | + | |
| Subject 2 | First Day | | | | Third Day | | | | | |
| 10 a.m. | 170 | 23.5 | 5.77 | | 370 | 5.5 | 6.61 | ..... | + | Five doses of |
| 12 m. | 75 | 24.0 | 6.01 | | 520 | 6.5 | 6.03+ | 1:100,000 | .. | methenamine, |
| 2 p.m. | 110 | 27.5 | 6.44 | | 425 | 20.0 | 5.58 | 1:35,000 | + | 15 grains, |
| 4 p.m. | 100 | 19.0 | 6.64 | | 430 | 17.5 | 5.50 | 1:30,000 | + | ammonium |
| 6 p.m. | 55 | 45.0 | 6.75 | | 140 | 66.5 | 5.65 | 1:20,000 | + | chloride, 15 |
| 8 p.m. | 145 | 22.5 | 5.98 | | 115 | 54.5 | 5.56 | 1:25,000 | + | grains, at 9, |
| 10 p.m. | 50 | 35.0 | 6.32 | | 330 | 23.0 | 5.69 | 1:35,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 370 | 28.5 | 6.18 | | 505 | 39.0 | 5.77 | 1:25,000 | + | |
| 24 hour average | 1,075 | 25.0 | 6.18 | | 2,732 | 25.5 | 5.77 | | | |
| | Second Day | | | | Fourth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 110 | 25.5 | 5.79 | 1:60,000 | + | |
| 10 a.m. | 225 | 5.5 | 7.14 | | 200 | 15.5 | 5.57 | 1:100,000 | + | |
| 12 m. | 80 | 11.0 | 7.08 | | 495 | 15.5 | 5.64 | 1:45,000 | + | Same dose |
| 2 p.m. | 175 | 17.0 | 6.80 | | 390 | 23.0 | 5.41 | 1:30,000 | + | |
| 4 p.m. | 490 | 6.0 | 6.90 | | 495 | 19.5 | 5.44 | 1:25,000 | + | |
| 6 p.m. | 75 | 26.5 | 6.74 | | 310 | 32.0 | 5.64 | 1:25,000 | + | |
| 8 p.m. | 205 | 9.5 | 6.66 | | 330 | 21.0 | 5.46 | 1:25,000 | + | |
| 10 p.m. | 445 | 3.0 | 7.43 | | 385 | 18.0 | 5.74 | 1:40,000 | + | |
| 6 a.m. | 465 | 14.0 | 6.47 | | 430 | 50.5 | 5.72 | 1:20,000 | + | |
| 24 hour average | 2,160 | 9.0 | 6.88 | | 3,145 | 24.0 | 5.63 | ..... | + | |
| | | | | | Fifth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 250 | 14.0 | 5.81 | 1:80,000 | + | Seven doses of |
| 10 a.m. | ... | .... | .... | | 390 | 10.0 | 5.48 | 1:100,000 | + | same sub- |
| 12 m. | ... | .... | .... | | 265 | 37.0 | 5.46 | 1:25,000 | + | stances at |
| 2 p.m. | ... | .... | .... | | 355 | 31.0 | 5.33 | 1:20,000 | + | 8:30, 10, 11:30, |
| 4 p.m. | ... | .... | .... | | 200 | 61.0 | 5.42 | 1:10,000 | + | 1, 3, 7, 9 |
| 6 p.m. | ... | .... | .... | | 95 | 96.5 | 5.51 | 1:10,000 | + | |
| 8 p.m. | ... | .... | .... | | 80 | 62.5 | 5.58 | 1:15,000 | + | |
| 10 p.m. | ... | .... | .... | | 165 | 59.0 | 5.65 | 1:25,000 | + | |
| 6 a.m. | ... | .... | .... | | 385 | 44.0 | 5.70 | 1:15,000 | + | |
| 24 hr. av. | ... | .... | .... | | 2,125 | 31.0 | 5.61 | ..... | + | |
| 8 a.m. | ... | .... | .... | | 265 | 11.0 | 5.36 | 1:60,000 | + | |

TABLE 2.—*Results of Experiment 2—Continued*

| Time | Volume | Titratable Acidity | $p_H$ | Remarks | Volume | Titratable Acidity | $p_H$ | Formaldehyde | Methenamine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject 3 | First Day | | | | Third Day | | | | | |
| 10 a.m. | 65 | 53.0 | 6.30 | | 245 | 12.0 | 6.80 | ..... | + | Five doses of |
| 12 m. | 75 | 25.5 | 6.73 | | 160 | 35.0 | 5.94 | 1:60,000 | + | methenamine, |
| 2 p.m. | 220 | 13.0 | 6.86 | | 130 | 55.0 | 5.99 | 1:50,000 | + | 15 grains, |
| 4 p.m. | 365 | 6.0 | 7.00 | | 200 | 40.5 | 6.02 | 1:60,000 | + | ammonium |
| 6 p.m. | 60 | 49.5 | 6.21 | | 380 | 26.5 | 5.79 | 1:50,000 | + | chloride, 15 |
| 8 p.m. | 230 | 10.5 | 6.98 | | 540 | 12.0 | 6.13 | 1:100,000 | + | grains, at 9, |
| 10 p.m. | 310 | 4.0 | 7.25 | | 125 | 42.0 | 5.87 | 1:45,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 405 | 23.5 | 6.01 | End of first day | 255 | 73.5 | 5.65 | 1:10,000 | + | |
| 24 hour average | 1,730 | 12.5 | 6.71 | | 2,035 | 27.5 | 5.97 | ..... | + | |
| | Second Day | | | | Fourth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 65 | 50.5 | 5.63 | 1:50,000 | + | |
| 10 a.m. | 115 | 20.0 | 6.69 | | 75 | 52.0 | 5.60 | 1:100,000 | + | |
| 12 m. | 80 | 29.5 | 6.68 | | 120 | 68.0 | 5.72 | 1:50,000 | + | Same dose |
| 2 p.m. | 280 | 13.5 | 6.47 | | 140 | 71.0 | 5.49 | 1:30,000 | + | |
| 4 p.m. | 85 | 57.0 | 5.94 | | 260 | 42.0 | 5.55 | 1:30,000 | + | |
| 6 p.m. | 95 | 39.0 | 6.13 | | 210 | 54.5 | 5.46 | 1:20,000 | + | |
| 8 p.m. | 145 | 15.0 | 6.64 | | 280 | 28.5 | 5.56 | 1:25,000 | + | |
| 10 p.m. | 240 | 6.0 | 7.08 | | 195 | 33.0 | 5.51 | 1:30,000 | + | |
| 6 a.m. | 155 | 64.5 | 5.68 | End of second day | 565 | 39.5 | 5.53 | 1:25,000 | + | |
| 24 hour average | 1,195 | 23.0 | 6.35 | | 1,910 | 41.0 | 5.63 | ..... | + | |
| | | | | | Fifth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 105 | 20.5 | 5.70 | 1:70,000 | + | |
| 10 a.m. | ... | .... | .... | | 320 | 18.0 | 5.63 | 1:70,000 | + | Same dose |
| 12 m. | ... | .... | .... | | 140 | 53.0 | 5.56 | 1:45,000 | + | |
| 2 p.m. | ... | .... | .... | | 120 | 73.5 | 5.43 | 1:25,000 | + | |
| 4 p.m. | ... | .... | .... | | 140 | 74.5 | 5.39 | 1:25,000 | + | |
| 6 p.m. | ... | .... | .... | | 70 | 84.0 | 5.14 | 1:30,000 | + | |
| 8 p.m. | ... | .... | .... | | 285 | 33.5 | 5.47 | 1:25,000 | + | |
| 10 p.m. | ... | .... | .... | | 420 | 17.0 | 5.56 | 1:30,000 | + | |
| 6 a.m. | ... | .... | .... | | 750 | 24.5 | 5.48 | 1:40,000 | + | |
| 24 hr. av. | ... | .... | .... | | 2,350 | 28.0 | 5.51 | ..... | + | |
| 8 a.m. | ... | .... | .... | | 70 | 53.5 | 5.41 | 1:100,000 | + | |

increasing the intake of ammonium chloride to 105 grains (6.82 Gm.). This perceptibly lowered the $p_H$, and the combined effect was to increase the concentration of urinary formaldehyde to the order of 1:25,000 or more, the early morning urine, in the case of F.D., showing a concentration of 1:15,000.

EXPERIMENT 3.—This is an experiment in which the subjects started on the same dosage as in experiment 1, with five doses of methenamine and ammonium chloride, so that during the day 37½ grains of the former and 75 grains of the latter were given. This was then raised on the third day to seven doses, giving a third intake of 52½ and 105 grains (3.43 and 6.82 Gm.), respectively. It can be observed at once from table 3 that at the 7½ grain level for methenamine, even at seven times a day, the urinary concentration of formaldehyde is far below that found in experiment 2 in which 15 grains of methenamine was given from five to seven times a day.

The difference in the effectiveness of 15 over 7½ grains of methenamine with 15 grains of ammonium chloride is shown in charts 1 and 2. In the first subject, F.D., on five doses per day, the concentration was raised from approximately 1:45,000 to 1:30,000 on the first day. On the second day the higher dose maintained 1:30,000, while with the lower dose the urine during a large part of the time showed ineffectual concentration. With seven doses, the higher intake

TABLE 3.—*Results of Experiment 3*

| Time | Volume | Titratable Acidity | $p_H$ | Remarks | Volume | Titratable Acidity | $p_H$ | Formaldehyde | Methenamine | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject 1 | First Day | | | | | | Third Day | | | |
| 10 a.m. | 90 | 49.0 | 5.66 | | 65 | 20.5 | 6.28 | ..... | + | Five doses of |
| 12 m. | 165 | 10.5 | 6.16 | | 90 | 43.5 | 5.62 | 1:60,000 | + | methenamine, |
| 2 p.m. | 540 | 4.5 | 6.74 | | 250 | 27.0 | 5.24 | 1:45,000 | + | 7½ grains, |
| 4 p.m. | 115 | 16.0 | 6.78 | | 90 | 63.0 | 5.48 | 1:45,000 | + | ammonium |
| 6 p.m. | 115 | 23.5 | 6.35 | | 105 | 67.5 | 5.43 | 1:40,000 | + | chloride, 15 |
| 8 p.m. | 270 | 7.0 | 6.68 | | 100 | 41.5 | 5.44 | 1:50,000 | + | grains, at 9, |
| 10 p.m. | 100 | 9.0 | 7.11 | | 100 | 49.0 | 5.53 | 1:40,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 245 | 29.5 | 6.27 | | 385 | 44.5 | 5.70 | 1:30,000 | + | |
| 24 hour average | 1,640 | 12.5 | 6.52 | | 1,185 | 40.5 | 5.69 | | | |
| | Second Day | | | | | | Fourth Day | | | |
| 8 a.m. | ... | .... | .... | | 70 | 37.0 | 5.85 | 1:70,000 | + | |
| 10 a.m. | 75 | 23.0 | 6.35 | | 80 | 51.5 | 5.77 | 1:100,000 | + | |
| 12 m. | 85 | 11.5 | 7.20 | | 95 | 59.0 | 5.62 | 1:40,000 | + | |
| 2 p.m. | 285 | 5.5 | 7.14 | | 200 | 46.5 | 5.36 | 1:35,000 | + | Same dose |
| 4 p.m. | 225 | 15.0 | 6.86 | | 115 | 70.5 | 5.46 | 1:40,000 | + | |
| 6 p.m. | 205 | 8.0 | 7.33 | | 75 | 77.5 | 5.43 | 1:45,000 | + | |
| 8 p.m. | 320 | 3.5 | 7.40 | | 130 | 46.0 | 5.48 | 1:40,000 | + | |
| 10 p.m. | 145 | 3.5 | 7.73 | | 120 | 97.5 | 5.61 | 1:50,000 | + | |
| 6 a.m. | 385 | 11.5 | 6.88 | | 315 | 51.0 | 5.68 | 1:40,000 | + | |
| 24 hour average | 1,625 | 8.0 | 7.12 | | 1,200 | 48.0 | 5.68 | | | |
| | | | | | Fifth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 70 | 51.5 | 5.74 | 1:100,000 | + | Seven doses of |
| 10 a.m. | ... | .... | .... | | 230 | 20.5 | 5.65 | 1:100,000 | + | same sub- |
| 12 m. | ... | .... | .... | | 230 | 31.0 | 5.56 | 1:40,000 | + | stances at |
| 2 p.m. | ... | .... | .... | | 370 | 27.0 | 5.27 | 1:30,000 | + | 8:30, 10, 11:30, |
| 4 p.m. | ... | .... | .... | | 185 | 53.5 | 5.20 | 1:25,000 | + | 1, 3, 7, 9 |
| 6 p.m. | ... | .... | .... | | 175 | 38.0 | 5.31 | 1:35,000 | + | |
| 8 p.m. | ... | .... | .... | | 195 | 26.5 | 5.25 | 1:40,000 | + | |
| 10 p.m. | ... | .... | .... | | 150 | 44.0 | 5.37 | 1:35,000 | + | |
| 6 a.m. | ... | .... | .... | | 230 | 59.0 | 5.46 | 1:50,000 | + | |
| 24 hr. av. | ... | .... | .... | | 1,835 | 33.5 | 5.48 | ..... | + | |
| 8 a.m. | ... | .... | .... | | 135 | 30.5 | 5.36 | 1:70,000 | + | |
| Subject 2 | First Day | | | | | | Third Day | | | |
| 10 a.m. | 225 | 4.0 | 7.02 | | 215 | 4.0 | 6.71 | ..... | + | Five doses of |
| 12 m. | 145 | 6.5 | 7.44 | | 205 | 27.5 | 5.80 | 1:80,000 | + | methenamine, |
| 2 p.m. | 115 | 15.0 | 7.40 | | 225 | 46.0 | 5.48 | 1:40,000 | + | 7½ grains, |
| 4 p.m. | 120 | 15.0 | 7.14 | | 135 | 64.0 | 5.56 | 1:35,000 | + | ammonium |
| 6 p.m. | 85 | 38.5 | 6.06 | | 175 | 47.0 | 5.53 | 1:35,000 | + | chloride, 15 |
| 8 p.m. | 85 | 25.0 | 6.63 | | 305 | 27.0 | 5.46 | 1:40,000 | + | grains, at 9, |
| 10 p.m. | 380 | 5.0 | 7.10 | | 350 | 18.5 | 5.85 | 1:60,000 | + | 11:30, 2, 4:30, 7 |
| 6 a.m. | 350 | 27.0 | 6.10 | End of first day | 580 | 35.5 | 5.82 | 1:40,000 | + | |
| 24 hour average | 1,505 | 12.0 | 6.80 | | 2,190 | 27.5 | 5.77 | ..... | + | |
| | Second Day | | | | | | Fourth Day | | | |
| 8 a.m. | ... | .... | .... | | 235 | 10.0 | 5.85 | 1:100,000 | + | |
| 10 a.m. | 180 | 3.0 | 7.20 | | 420 | 13.0 | 5.37 | 1:100,000 | + | |
| 12 m. | 120 | 13.5 | 6.64 | | 195 | 36.0 | 5.58 | 1:40,000 | + | Same dose |
| 2 p.m. | 110 | 20.5 | 6.85 | | 125 | 73.0 | 5.51 | 1:35,000 | + | |
| 4 p.m. | 125 | 18.5 | 6.86 | | 160 | 67.0 | 5.55 | 1:35,000 | + | |
| 6 p.m. | 95 | 33.5 | 6.34 | | 150 | 61.5 | 5.49 | 1:30,000 | + | |
| 8 p.m. | 50 | 37.0 | 6.26 | | 385 | 24.5 | 5.44 | 1:35,000 | + | |
| 10 p.m. | 175 | 4.0 | 7.07 | | 300 | 24.5 | 5.79 | 1:45,000 | + | |
| 6 a.m. | 440 | 19.0 | 6.00 | End of second day | 790 | 22.5 | 6.09 | 1:70,000 | + | |
| 24 hour average | 1,295 | 13.5 | 6.54 | | 2,750 | 26.5 | 5.76 | ..... | + | |
| | | | | | Fifth Day | | | | | |
| 8 a.m. | ... | .... | .... | | 180 | 13.0 | 5.75 | 1:100,000 | + | |
| 10 a.m. | ... | .... | .... | | 105 | 23.5 | 5.31 | 1:100,000 | + | Seven doses of |
| 12 m. | ... | .... | .... | | 365 | 27.5 | 5.49 | 1:30,000 | + | same sub- |
| 2 p.m. | ... | .... | .... | | 230 | 52.0 | 5.42 | 1:25,000 | + | stances at |
| 4 p.m. | ... | .... | .... | | 295 | 41.0 | 5.37 | 1:25,000 | + | 8:30, 10, 11:30, |
| 6 p.m. | ... | .... | .... | | 190 | 58.0 | 5.42 | 1:25,000 | + | 1, 3, 7, 9 |
| 8 p.m. | ... | .... | .... | | 240 | 36.0 | 5.54 | 1:40,000 | + | |
| 10 p.m. | ... | .... | .... | | 320 | 24.5 | 5.78 | 1:60,000 | + | |
| 6 a.m. | ... | .... | .... | | 730 | 24.5 | 5.56 | 1:45,000 | + | |
| 24 hr. av. | ... | .... | .... | | 2,655 | 29.5 | 5.56 | ..... | + | |
| 8 a.m. | ... | .... | .... | | 520 | 17.0 | 5.64 | 1:45,000 | + | |

of methenamine showed a concentration of 1:20,000 well sustained. In all cases, the two hour period in the morning gave urine of low formaldehyde concentration.

In the case of W.B., shown in chart 2, the advantage of the higher dose is not so pronounced but is evident from the curves.

Chart 3 shows the close relationship of the $p_H$ curve to the concentration of formaldehyde in the case of E.G., and explains the low

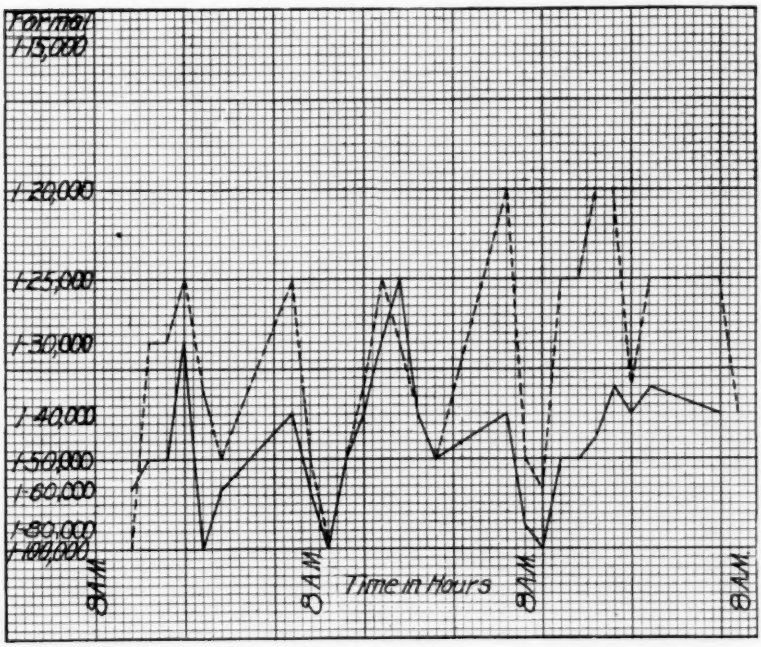


Chart 2.—The advantage of the higher dose is not so pronounced, but is evident from the curves. The broken line represents the results from 75 grains; the solid line, from 37½ grains.

concentration of formaldehyde at some periods as being due, not to an insufficiency of the acidifying factor, but to lack of available methenamine.

Chart 4 shows what may be expected of ammonium chloride as a urinary acidifier in 15 grain doses. This curve is not scaled to hydrogen ion concentration but to the $p_H$ scale which dwarfs the increased acidity as represented by the curve.

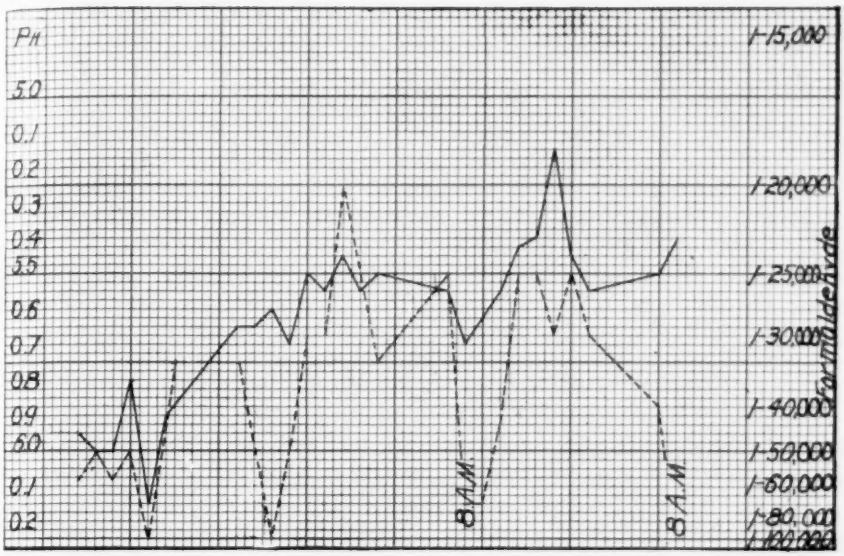


Chart 3.—Close relationship of the $p_H$ curve to the concentration of formaldehyde in the case of E. G., experiment 2. The chart shows the low concentration of formaldehyde as due to the lack of methenamine. The broken line represents the formaldehyde; the solid line, the $p_H$. Each small square represents one hour.

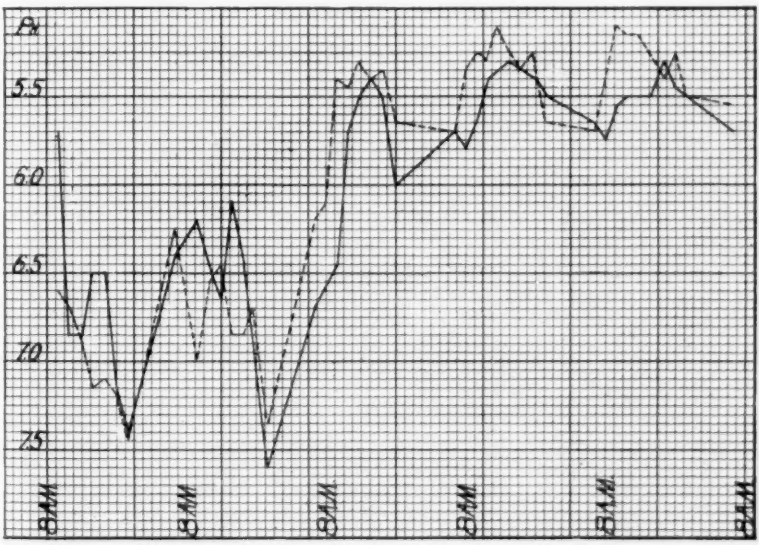


Chart 4.—The effect of ammonium chloride as a urinary acidifier. The broken line represents the results for F.D.; the solid line, for W.B. Each small space represents one and a half hours.

SUMMARY

Ammonium chloride, even against the high buffering effect of nearly neutral urine, produces a rapid acidifying effect, which at a level of 15 grains five times a day showed a $p_H$ of about 5.5.

Methenamine at a level of 7½ grains five times a day gave a concentration somewhat but not proportionately lower than that found at the dosage of 15 grains. The acidity is of prime importance.

In this work the dosage of methenamine varied from 37½ to 105 grains a day. The higher doses gave the higher concentration of formaldehyde, other factors being equal. Ammonium chloride did not yield the maximum acidifying effect until the second day.

Following the last dose in the evening, the concentration of formaldehyde fell somewhat but usually became higher during the night, owing to the length of time the urine remained in the bladder. The sample taken at 6 a. m. usually had a high formaldehyde concentration, since most of the methenamine had been excreted during the night.

There is a marked drop in the formaldehyde concentration in the forenoon, but it rises rapidly as the excretion of methenamine is increased following the medication.

# THE RELATION OF WITHDRAWAL OF CEREBROSPINAL FLUID TO THE BODY TEMPERATURE: CONSIDERATION OF A THERMOREGULATORY CENTER

## A STUDY OF TWO HUNDRED AND FIFTY CASES *

ALFRED GORDON, M.D.
PHILADELPHIA

During the course of routine examinations of the spinal fluid in neuropsychiatric patients, the following peculiarity was observed, at first accidentally: Shortly after lumbar punctures, a few patients complained of general discomfort. This circumstance led the nurses in attendance to take the temperatures of these patients. They found a slight elevation. Interested by this incidental observation, I decided to pursue this investigation further and thus commenced to gather observations on a large scale. The observations on 250 cases presented here suggest certain ideas concerning the pathogenesis of fever and the possible localization of a thermoregulatory center. The observations in adults differ somewhat from those in children. The adult group consisted of twenty-five patients with hemiplegia, five with increased intracranial pressure, seventeen with idiopathic epilepsy, ten with meningitis, forty with psychoneuroses, twelve with manic-depressive psychosis, ten with transverse myelitis, two with multiple sclerosis, fifteen with paresis, twenty with tabes, forty with severe headache of syphilitic origin and four with dementia praecox. The fifty children included ten with meningitis, fifteen mentally defective, twenty with epilepsy and five with Little's disease.

The temperature of each patient was taken immediately before, and five minutes, half an hour, one hour and three hours after the puncture of the spinal canal or of the lateral ventricles in the brain. In the adult series, the rise commenced in the majority of cases five minutes, and in some cases only thirty minutes, later. It continued to ascend until the third hour; then it gradually descended to reach the degree at which it stood before the punctures (chart 1). The highest rise was 2 F. and the lowest 0.5. The greater the amount of spinal fluid withdrawn, the higher the temperature went up and the sooner the rise commenced. It was exceedingly interesting to observe that whenever spinal fluid could not be obtained on one and even on several attempts—which not infrequently happens and which usually means no penetration of the needle into the dural sac—in every such case, no change in the

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* Read before the College of Physicians on Nov. 7, 1928.

bodily temperature could be noticed. In five cases with the diagnosis of serous meningitis (judged by the typical clinical symptoms and absence of specific micro-organisms) there was a slight fever before the lumbar puncture, but the withdrawal of spinal fluid was followed by a greater rise (from 1 to 2.5 degrees) than in the afebrile cases (charts 2 and 3). The following interesting observation deserves special men-

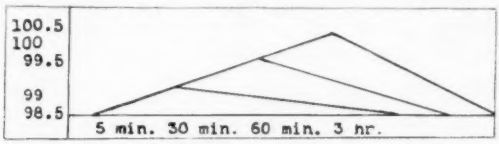


Fig. 1.—The rise in bodily temperature following lumbar puncture.

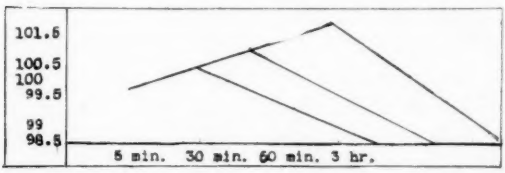


Fig. 2.—The rise in bodily temperature following lumbar puncture in serous meningitis.

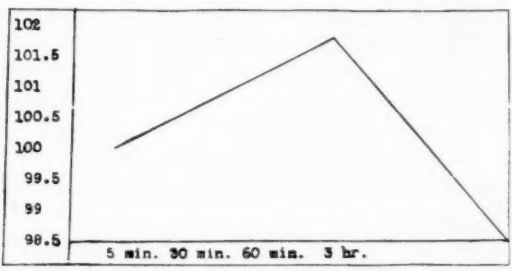


Fig. 3.—The rise in bodily temperature following lumbar puncture in febrile cases.

tion since it apparently has a certain bearing on the pathogenesis of fever, which will be discussed later. In cases of evident meningeal irritation and especially in cases of seropurulent spinal fluid in which a definite or specific micro-organism cannot be determined, I am in the habit of injecting physiologic solution of sodium chloride following the withdrawal of spinal fluid. In the majority of such cases, I have not observed a rise but an immediate fall of the temperature after the evacuation of some of the spinal fluid, but a rapid subsequent ascension

of the temperature occurs after this solution has replaced the seropurulent fluid (chart 4). Moreover, this rise is greater (2 degrees) than in the cases in which lumbar puncture is employed alone.

In several cases of puncture of the lateral ventricles, either for ventriculography or for the alleviation of epileptic convulsions,[1] the removal even of a small quantity of cerebrospinal fluid, such as 5 or 10 cc., was followed by a rise of temperature and this, curiously enough, much sooner than in the case in which lumbar puncture was made.

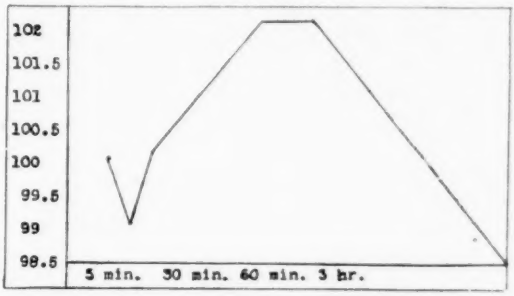


Fig. 4.—The rise in bodily temperature following lumbar puncture and injection of physiologic solution of sodium chloride in febrile cases.

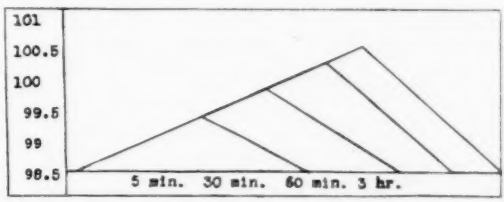


Fig. 5.—The rise in bodily temperature following ventricular puncture.

namely, in two or three minutes (chart 5). As in the cases in which lumbar puncture was done, the larger the quantity of fluid withdrawn, the higher was the elevation of temperature. When the removal of the fluid was followed by an injection of air for ventriculography or of physiologic solution of sodium chloride, as in some meningeal conditions, the rise of the temperature was more marked than in the cases without the secondary introduction of air or fluid into the ventricles (chart 6). It must be mentioned also that the duration of the elevated

1. Gordon, Alfred: Hydrocephalus with Cessation of Persistent Convulsions after Puncture of the Lateral Ventricles, J. A. M. A. **88**:1234 (April 16) 1927.

temperature is greater in the cases of ventricular than in the cases of lumbar puncture, being as long as three or four or even five hours.

The children presented, in general, the same picture as the adults with the exception, however, that under identical circumstances and in identical pathologic conditions they invariably showed a rise of temperature decidedly highert than did the adults: When the latter showed a rise of 0.5 degree, the children showed a rise of 1 degree; when the adults presented a rise of 1 degree, the children presented a rise of 1.5 degrees.

In each of the two groups there were some differences in the intensity and rapidity of the reaction to the withdrawal of cerebrospinal fluid. For example, in the epileptic and meningeal patients there was

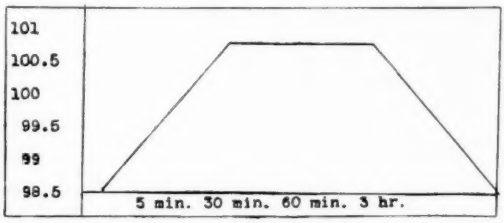


Fig. 6.—The rise in bodily temperature following ventricular puncture and injection of air.

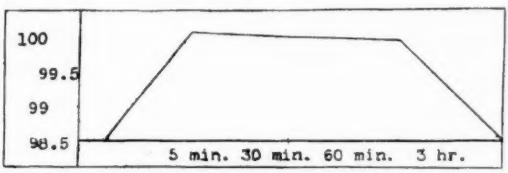


Fig. 7.—The rise in bodily temperature following ventricular or lumbar puncture in syphilitic headache.

a quicker and greater response to punctures than in the patients who were hemiplegic. Among those with psychoses, the rise of temperature was more marked in the maniacal phases than in the depressive phases, and in the patients with manic-depressive insanity, in general, the rise was greater than in the patients with psychoneuroses. The duration of the higher temperature presented analogous differences. Patients with syphilitic headache presented an earlier, more prolonged and more marked reaction to punctures than those with tabes or those with paresis (chart 7). As to the latter two groups, the paretic patients were more conspicuous in their reaction than the tabetic ones. A more detailed account of some of these differences is presented in the charts.

COMMENT

In summing up these facts, special attention is invited to the following considerations, which in my opinion possess a special meaning. What is the reason that a dry puncture is not followed by an elevation of temperature? What is the reason that in cases of meningitis the preexisting febrile state becomes accentuated after a lumbar puncture? What is the reason that in cases of seropurulent cerebrospinal fluid the removal of some of it is followed by hypothermia, but as soon as a physiologic solution of sodium chloride is injected into the dural sac, the temperature rises? Although these phenomena cannot all be explained to full satisfaction, one fact nevertheless stands out and that is, a change in the stability or in the equilibrium of the cerebrospinal fluid, brought about by either ventricular or lumbar puncture and resulting in diminution of the quantity of the cerebrospinal fluid, produces a change in the bodily temperature. If this is so, the next question is: "By what mechanism?" Schoenfeld [2] showed that the removal even of a small quantity of spinal fluid is followed by an increase in its cells and albumin contents. On this basis, one may argue that the mechanical irritation of the meninges produced by the puncture of the dural sac results in chemical and physical changes of the fluid and consequently in hyperthermia. On the other hand, one should also take into account the meningeal irritation per se produced at the time of the puncture and consider it, also, as one of the causative elements in the rise of temperature. Indeed, the observations of Thurzo and Nagy [3] indicate this possibility.

So far my discussion of the cause of the fever leads to consideration of two factors; namely, mechanical stimulation and meningeal irritation.

Auerbach [4] calls attention to the fact that an abundant loss of cerebrospinal fluid during an operation on the brain and spinal cord is frequently associated with a rise of bodily temperature. This observation, as well as those of Jakobi and Roemer,[5] of Trendelenburg [6] and of Jánossy and Horvath,[7] suggests a new possibility; namely, that pituitary secretions, which have been found in cerebrospinal fluid, cause the increase of bodily temperature during physical disturbances of this fluid. Whether this assumption is correct or not, it is impossible at present to ascertain.

2. Schoenfeld: Deutsche Ztschr. f. Nervenh., 1919, p. 64.
3. Thurzo and Nagy: Deutsche Ztschr. f. Nervenh., 1923, p. 374.
4. Auerbach: Ztschr. f. d. ges. Neurol. u. Psychiat. **24**:229, 1922.
5. Jakobi and Roemer: Arch. f. exper. Path. u. Pharmakol., 1912, p. 149.
6. Trendelenburg: Klin. Wchnschr. **3**:777, 1924.
7. Jánossy and Horvath: Zentralbl. f. d. ges. Neurol. u. Psychiat., 1926, p. 820.

The outstanding feature in all observations recorded is that when the physical relationship of the cerebrospinal fluid is disturbed in one way or another, the bodily temperature is equally disturbed. At this juncture, I may mention also the following occurrence: In one case of progressive muscular atrophy of syphilitic origin and in one case of hydrocephalus, the physicians in charge drained the spinal canal to the maximum. In each case, the body temperature rapidly became low (97 F. and 96 F., respectively).

In the presence of such facts, as well as of those mentioned previously, one is firmly led to the conception that not only is there a relationship of the cerebrospinal fluid to changes in the temperature but this fluid is actually in some relationship to a thermoregulatory center. That the central nervous system, generally speaking, has a direct influence on the bodily temperature is well recognized. Experimental physiology has demonstrated the existence of a "thermic center." From among the vast number of observations in this field, suffice it to recall the experiments of Citron and Leschke,[8] who showed conclusively on dogs that the midbrain contains a thermic center. They infected the animals, the temperatures naturally rose, and then they sectioned the midbrain. No fever was thereafter in evidence. Isenschmid, Krehl and Schnitzler[9] concluded from their own observations that the midbrain and, precisely, the tuber cinereum, play an important rôle in thermoregulation. The adjacent area, especially the floor, of the third ventricle is the most probable center of the regulation of bodily temperature. A further step was made in the more accurate localization of such a center, when Jacobi and Roemer[5] announced that not only a direct irritation of the walls of the ventricle, but also a transmission of a contiguous disturbing influence to them is apt to influence the bodily temperature. If one considers that there is a close relationship between the cerebrospinal fluid at any level within the brain, on the surface of the brain or in the spinal canal with the third ventricle (namely, by means of an anatomic communication of the lateral ventricles with the third through the foramen of Monro, of the fourth with the third through the aqueduct of Sylvius, of the fourth ventricle with the cisterna magna through the foramina of Magendie and Luschka and finally, of the cisterna with the spinal canal without an intermediary passage-way); if one also considers the fact that the cisterna magna is the area into which the fluid flows from every direction of the brain and which is therefore in a certain relationship to smaller collections of fluid at the base of the brain and also to that in the subarachnoid spaces on the surface of the brain; if, finally, one

8. Citron and Leschke: Verhandl. d. Kong. f. inn. Med. **30**:65, 1913.

9. Isenschmidt; Krehl, and Schnitzler: Arch. f. exper. Path. u. Pharmakol., 1912, p. 109; 1914, p. 202.

recognizes the close connection of fluid contents between the ventricular systems, the surface of the brain and the spinal canal, one can readily conceive that a physical disturbance of the fluid in the cerebrospinal system at one of its levels is bound to produce a more or less intense mechanical effect on the same fluid at other levels. If one also recalls the afore mentioned experiments of Citron and Leschke on the midbrain, as well as of others on the area surrounding the third ventricle, one can readily understand the hyperthermia provoked by the lumbar or the ventricular puncture.

The walls of the ventricles are the only places in the central nervous system where the cerebrospinal fluid is in intimate contact with the parenchyma of nervous tissue; they are therefore physiologic centers. It stands to reason that any physical disarrangement taking place in the cerebrospinal fluid will cause a corresponding irritation of the ventricular walls and therefore of the thermic center. Removal of some fluid may produce a change in the shape or in the general configuration of the ventricle or a collapse of its walls, or else it may be the point of departure for reformation of the fluid within the emptied ventricle, which, as is well known, is a rapidly developing phenomenon when the ventricles are in a pathologic state.

Auerbach,[4] as stated, among many others, observed a rise of temperature during operative procedures on the cranium or on the spinal cord, which, of course, are usually accompanied by a considerable loss of cerebrospinal fluid; the hyperthermia subsided when the fluid had again reached its normal level.

It was mentioned that in two cases an erroneous maximal removal of the spinal fluid was followed by a lowering of the bodily temperature. A low temperature has been observed in intracerebral hypertension, in hydrocephalus and in traumatic injuries of the cervical cord. In all such cases, an undue pressure is undoubtedly transmitted to the fourth ventricle and to the cervical cord. This pressure, physiologically speaking, means interruption of the central and peripheral pathways the function of which is to regulate the bodily heat. That such pathways exist has been demonstrated repeatedly. Suffice it to mention the investigation of Freund and Grafe [10] among many others.

Whether or not one considers the rise or the fall of the bodily temperature in the course of manipulations of the cerebrospinal fluid irrespective of different circumstances under which individual variations are observed, the fact remains that a mechanical withdrawal of a certain amount of fluid has an influence on the bodily temperature. In other words at that time the thermoregulatory centers are disturbed. Since the cerebrospinal fluid takes its origin in the choroid plexuses

10. Freund and Grafe: Arch. f. exper. Path. u. Pharmakol., 1912, p. 135.

or in the ependyma or in both, it is the interior of the ventricles or more precisely the ventricular walls that are of special importance in the regulation of the bodily temperature. Dilatation, narrowing or some other alteration in the configuration of the ventricles, which can all be brought on by physical manipulations of the cerebrospinal fluid, such as punctures of the ventricles or of the spinal canal, produces a mechanical irritation of the blood vessels and nerve-endings in ventricular walls and consequently a change in the bodily temperature. All experimental investigations indicate the third ventricle as playing the most important rôle in thermic regulation. There are several problems in this direction which require greater elaboration, such as the reformation of the fluid, the change in the chemical contents in the cerebrospinal fluid during physical manipulations of it, the question of a localized meningitis during punctures and finally the individual variations in the rise or the fall of temperature. Further research is indicated for the solution of these problems. The object of the present work, however, has been merely to call attention to the fact that in alterations of bodily temperature of so-called cerebral origin, disturbances in the physical relationship of the cerebrospinal fluid plays an important, if not paramount, rôle. While the subject under discussion pertains to the domain of pathologic physiology, nevertheless the practical side of it, namely, the diagnostic and prognostic value, cannot be ignored.

## SUMMARY

Two hundred and fifty patients presenting a great variety of nervous and mental disorders were submitted to lumbar and ventricular punctures. There were a group of adults and a group of children. The bodily temperature of each patient was taken before and several times within three hours after the puncture. Elevation of temperature commenced a few minutes after every such manipulation. In some cases, physiologic solution of sodium chloride was injected in lieu of the withdrawn cerebrospinal fluid. When the punctures were dry (no fluid obtained), the temperature remained unaltered. These observations, including those concerning the variation in the degree of the elevated temperature, indicate that a change in the stability or in the equilibrium of the cerebrospinal fluid brought about by either ventricular or lumbar puncture produces a change in the bodily temperature.

## CONCLUSIONS

The present study as well as the casual observations made by some other investigators, especially by those who, for one reason or another, had to manipulate the cerebral ventricles or the spinal canal, leads to the following conclusions:

1. There is a relationship between the cerebrospinal fluid and the changes in the bodily temperature.

2. The fluid is actually in some relationship to a thermoregulatory center.

3. Ventricular or spinal withdrawal of fluid produces an alteration in the configuration of the ventricles and consequently an irritation of the nerve-endings in the ventricular walls.

4. The third ventricle plays the most conspicuous part in thermic regulation.

# THROMBO-ANGIONECROTIC CHANGES OF THE KIDNEYS IN CHRONIC NEPHRITIS *

BERNARD STERNBERG, M.D.
BROOKLYN

Classification of the anatomic changes in what appears clinically to be chronic nephritis is made difficult by the variety and peculiarity of the anatomic lesions found in the kidneys. From a purely morphologic point of view, the renal changes can be divided into two main groups: (1) inflammatory changes involving primarily the glomeruli or the tubular parenchyma or both, and (2) changes involving primarily the vascular apparatus, with other changes occurring apparently secondarily. While the former condition, the nephritis sensu strictu, is easy to understand, the greatest difficulties are met with in the interpretation of the vascular renal disease.

According to the latest anatomic work in this line, vascular changes of the kidneys are to be classified, according to the size of the arteries involved, into arteriosclerotic and arteriolosclerotic changes. In the first, large discrete foci of atrophy are found with no impairment of renal function. In the arteriolosclerotic type, the individual foci of atrophy and concomitant sclerosis are smaller but more numerous, and are therefore often coalescent. Their steady advance leads finally to the impairment of renal function.

In a certain group of cases, however, the anatomic observations, as well as the clinical picture, deviate substantially from those of ordinary arteriolosclerotic nephrosclerosis. These cases have been spoken of as "malignant nephrosclerosis" (Fahr [1]), "combination form" (Volhard, Fahr) and "nephrocirrhosis arteriolosclerotica progressa" (Aschoff,[2] Loehlein [3]).

Several cases studied during the last few years in the laboratory of the United Israel Zion Hospital seem to shed some light on this

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* From the Department of Laboratories, United Israel Zion Hospital.

1. Fahr, Thomas, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, no. 1, p. 405.

2. Aschoff: Ueber den Begriff der "Nephrosen und Sklerosen," Deutsche med. Wchnschr. **43**:43, 1917.

3. Loehlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Niere und ihre Bedeutung für die Nephritis, Leipzig, S. Hirzel, 1906; Zur Nephrocirrhosis Arteriolosclerotic, Med. Klin. **12**:136, 1916.

peculiar condition. Clinically, as well as morphologically, they are so similar that it is sufficient to report only one in detail.

REPORT OF CASE

*History.*—A. B., a girl, aged 18, was admitted to the hospital on March 1, 1928, complaining of headache, vomiting and weakness. She had had rheumatism, and tonsillectomy was performed at the age of 7. She had suffered from nocturia and polyuria. These symptoms, which had been present for some months, became aggravated just prior to her admission to the hospital, and her vision became blurred.

*Examination.*—On physical examination, she appeared thin and apathetic. The teeth were in bad condition and the throat was injected. Both retinas were edematous, and both disks were markedly choked. There was a blowing murmur at the apex of the heart. The apex was just outside the nipple line. The aortic second sound was greater than the pulmonic second sound. There were no other positive observations.

Her temperature on admission was 99.5 F.; it rose to 101.5 on March 3, rising gradually, and reached 105 before death. The pulse rate was 130, and the respiration rate was from 25 to 30. Blood pressure, systolic, was 220; diastolic, 130.

The urine showed albumin, 3 plus. The blood count showed hemoglobin, 65 per cent; red blood cells, 3,150,000; white blood cells, 14,800, with polymorphonuclear leukocytes 91 per cent and lymphocytes 9 per cent. The blood chemistry was: urea nitrogen, from 88 to 110 mg.; dextrose, from 100 to 140 mg., and creatinine, from 8 to 8.8 mg. The blood culture was negative.

The symptoms became progressively worse. She became unconscious, and died on March 7, 1928.

*Necropsy.*—At necropsy, a few drops of fluid were found in the pericardial sac. The pericardium was dull, and the epicardium on top of the auricles, particularly on the right side, was covered with fine grayish-red fibrinous membranes, which could readily be scraped off. The heart was the size of a huge man's fist. Its enlargement was eccentric, as the right side of the heart was a mere appendix to the left side. The musculature was pale reddish brown with areas of grayish yellow. These were most conspicuous underneath the epicardium, where they formed an irregular zone of foci of various sizes and shapes. The valves were thin and smooth. The aorta was of normal caliber. Its intima was smooth. The wall of the coronary arteries was slightly thickened and seemed to be somewhat more rigid.

The kidneys were rather small. Their capsules stripped off with difficulty, owing to discrete adhesions, which were particularly present about the poles. The greater part of the surface of the kidneys was smooth, except around the poles, where it was irregular owing to depressions and nodular projections. On section, the color of the kidneys was reddish gray.

In the cortex, several dark red foci were found, some of which were wedge-shaped, with their bases turned toward the capsule. The parenchyma of the cortex, particularly between the medullary pyramids, was mottled with yellow.

Both renal pelves were distended, and various calices, particularly those corresponding to the poles, were dilated. In these areas, the kidney substance was thin and did not reveal its normal structure.

The arteries leading to these impaired areas showed a rigid wall and patent lumen, while the rest of the renal arteries were thin and collapsed readily.

The other organs did not show any unusual features on gross examination.

*Diagnosis.*—The diagnosis was: subacute hemorrhagic glomerulonephritis; scattered arteriosclerotic atrophy of the kidneys; hypertrophy of the left side of the heart; passive congestion of the liver; lipoidosis of the suprarenal cortex; acute pericarditis; edema of the lungs.

*Microscopic Observations.*—On low power examination, the kidney presented several areas of necrosis. Most of these areas were pyramidal, with their bases on the capsule of the kidney, and their apexes reaching into the medulla. In some of these areas, little of the original structure was left. In others, it was merely the tubular epithelium and particularly the nuclei which showed disintegration. The lumina of the tubules were filled with a homogeneous mass. A similar exudate could also be seen within the capsules of the glomeruli. The stroma of these areas showed infiltration by leukocytes.

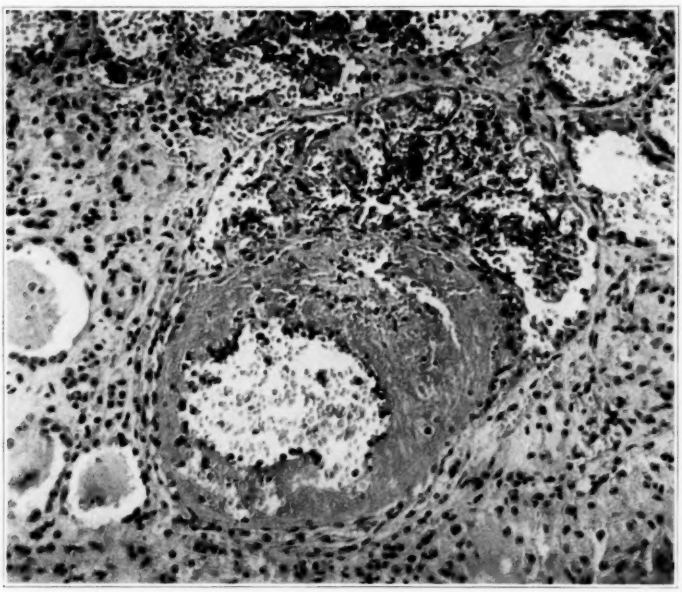

Fig. 1.—Thrombo-angionecrosis with aneurysmal dilatation of the afferent vessel. The picture shows a crescent-shaped compressed glomerulus on top of the vessel. Zeiss objective A; eyepiece K20.

In addition to these triangular areas, other areas of necrosis were scattered through the deeper portions of the cortex and the medulla, which showed similar changes. These were narrow strips, perpendicular to the surface of the kidney.

The other changes found in the kidney pertained to the glomeruli, tubules and blood vessels.

The glomeruli, outside of the necrotic areas, were comparatively well maintained. There were numerous glomeruli with patent, blood-filled loops without any changes in their capsules. Other glomeruli, however, revealed homogenization of part of their tufts, the loops of which were apparently not permeable. The homogeneous material stained much more intensely with eosin than the rest of the

Fig. 2.—Necrosis of an interlobular renal artery with thrombosis (longitudinal section). Incomplete infarction of surrounding parenchyma. Leitz apochromate 16 mm.; eyepiece 4.

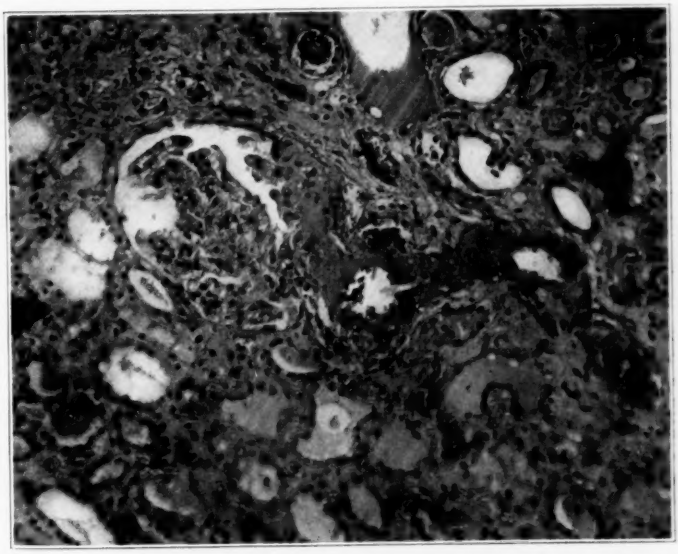

Fig. 3.—Necrosis of the afferent vessel with beginning dilatation; partial necrosis of the glomerulus. Polymorphonuclears are present in the necrotic areas. Zeiss objective A; eyepiece K20.

tissue. In other glomeruli there was definite evidence of nuclear injury, in addition to the hyalinization. The absence of endothelial cells and the presence of nuclear débris gave the impression of necrosis. In such areas a few leukocytes were usually present.

The tubular epithelium, outside of the necrotic areas, showed a great number of low cuboidal forms. Most of the tubules were wide. Some contained a homogeneous colloid material, which filled the whole lumen like a cast. Others contained droplets of globular material, which was also homogeneous and tended to coalesce. Casts were also found in the tubules of the medulla. They were of the same colloid type. Red cells were occasionally intermingled wtih the colloid material.

The changes of the arteries were particularly impressive. Both large and small arteries showed proliferation of the intima. The newly formed cells were

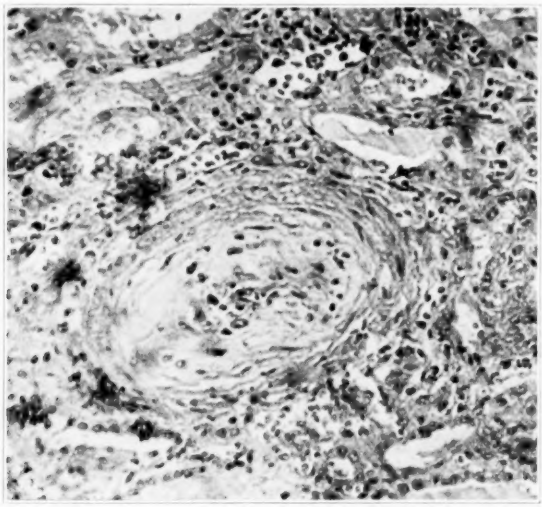

Fig. 4.—Obliterative endarteritis of an interlobular renal artery. The absence of hyalinization and the presence of polymorphonuclears are to be noted. Zeiss objective A; eyepiece K20.

large and contained a great amount of lipoid substance. Hence, they appeared vacuolated. The lumen of the arteries was considerably narrowed and frequently completely obliterated.

The elastic fibrils were hyperplastic. There was no doubling of the internal elastic membrane. On the other hand, the old elastic membrane was occasionally interrupted, and the defect replaced by cellular proliferation. The arterioles showed definite changes. A number of these small vessels were transformed into homogeneous hyaline masses, which appeared on cross-section like intensely eosinophilic rings with a narrow lumen. In others, the hyaline masses, replacing parts of the wall, alternated with granular débris, in which fragments of nuclei, particularly of polymorphonuclear leukocytes, were conspicuous. Polymorphonuclears were found both in the lumen of these vessels and around their external surface.

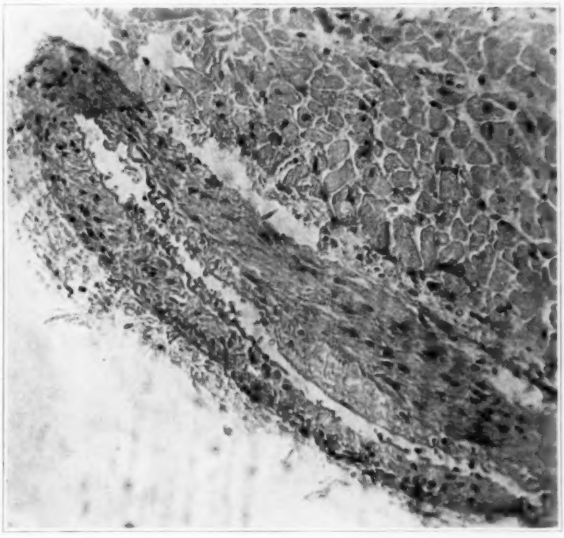

Fig. 5.—Subepicardial artery showing circumscribed focus of proliferation of intima and necrobiotic changes of the media. Leitz apochromate 8 mm.; eyepiece 4.

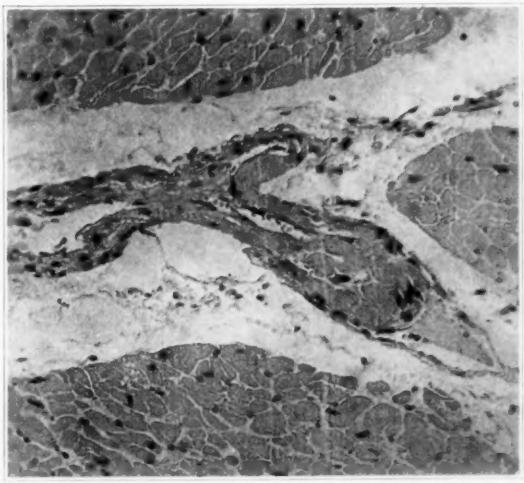

Fig. 6.—Myocardial artery showing extensive necrosis of the wall and partial obstruction of the lumen. Leitz apochromate 8 mm.; eyepiece 4.

Some of these arterioles could be followed to the glomeruli, the lesion continuing to the vasa afferentia, and then to the glomerulus proper, producing in the tufts the changes heretofore described. Some of the arterioles were thrombosed. The structure of the thrombus was granular or hyaline. Leukocytes could be seen within the thrombus. The wall of these arterioles was markedly necrotic.

The lesions of the arteries and arterioles were not restricted to the kidney. Other organs showed arterial lesions similar to those described, although somewhat less marked, namely, the spleen, the pancreas and particularly the myocardium.

Some of the smaller arteries of the heart showed nothing more than hyperplasia of the cells of the intima with eccentric narrowing of the lumen. Lipoidal deposits accounted for the vacuolization of these cells. The elastic membrane split about these areas, producing substantial defects. In other vessels, the proliferation was less marked, but there was evident necrosis of parts of the vessel

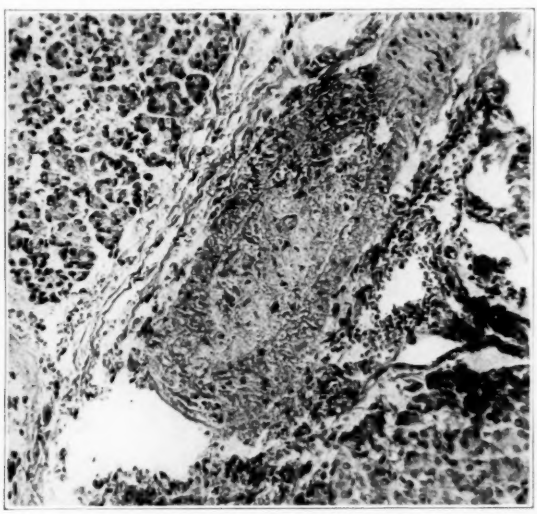

Fig. 7.—Pancreatic artery showing thrombosis with beginning organization, necrosis of the musculature and leukocytic infiltration. Leitz apochromate 8 mm.; eyepiece 4.

wall; that is, homogenization, fragmentation of the fibrils and exudate, collected into granular lumps, disappearance of the nuclei by karyorrhexis or lysis and the appearance of polymorphonuclears. Some of the latter broke down, producing nuclear débris. Around some of these vessels, infiltration of the perivascular connective tissue by polymorphonuclears could be observed. Such infiltrations were particularly extensive in the intralobular stroma of the pancreas, adjacent to the pancreatic arteries, with lesions similar to those described.

## COMMENT

The most significant features in this case were the changes in the blood vessels. These changes could be divided into two groups. The first group, representing apparently the older lesion, appeared to be

simply productive. These consisted of proliferation of the intima, with narrowing and occasionally occlusion of the lumen. The outer coats of the vessels were also involved. There was considerable production of collagenous fibrils in the adventitia, and a loss of musculature in the media with substitution of connective tissue. The elastic elements were also involved. There was a splitting up of the internal elastic fibrils. Deposits of lipoids in the cells of the proliferated intima were abundant. Necrosis or calcification was not a feature of the process, nor was hyalinization of the thickened intima. Thus, the changes resembled more those of chronic inflammation than those of arteriosclerosis.

The changes in the other group were much more recent. They were essentially alterative, including, as they did, necrosis and hyalinization. Acute exudative inflammatory changes, such as the migration of leukocytes and the appearance of an albuminous exudate, were concomitant. Thrombosis of some of the capillaries and arterioles completed the picture.

These changes were especially characteristic and were essentially different from the secondary changes of the glomeruli in ordinary arteriolosclerosis. The difference was sufficient to justify the assertion that the pathogenesis of these lesions was also different. This contention was substantiated by the changes in the arteries outside of the kidneys which were of the same character as those observed in the renal arterioles and capillaries. The changes of the glomeruli, moreover, were practically identical with what has been described repeatedly in cases of severe toxic and septic conditions and interpreted as a toxic or bacterial focal glomerulonephritis. The focal distribution of such lesions is their chief characteristic in contrast with the ordinary glomerulonephritis, in which all the glomeruli and every loop of each golmerulus is involved. The inflammatory character and the toxic or bacterial pathogenesis of these lesions are well established.

It therefore seems that the lesions in this case are entitled to the same interpretation. The presence of the chronic endarteritic changes with subsequent lesions of the kidney do not contradict the statement.

The main question is whether the more acute focal lesions occurred simply incidentally with the chronic vascular condition, or whether they were dependent on the latter. It is conceivable that a preceding disease of the arterioles was responsible for the focus of minor resistance which facilitated the onset of the acute lesion. On the other hand, the inflammatory character of the chronic arteriolar changes suggests the possibility that both the chronic lesion and the acute lesion were due to the same or similar causes, the acute changes representing an exacerbation of the chronic process.

In fact, cases of the type reported here usually occur in much younger persons than do cases of ordinary arteriolosclerosis. The age of the patient was 18, and the material on which this study is based includes a case in a patient aged 21, and two cases in patients less than 30. According to Fahr's statistics, persons subject to ordinary arteriolosclerosis are above 50 years of age, and the majority are above 60. The patients to whom he refers as having malignant sclerosis die at an age below 60 and almost one third of them die before 40. The predisposition of younger persons toward this condition is a strong argument against the conception that it is only a complication of ordinary arteriosclerosis. One is justified in disconnecting such cases of so-called malignant sclerosis from the ordinary arteriolosclerosis. As a suitable name for this condition, I suggest the term renal thrombo-angionecrosis or, in cases of advanced contraction of the kidneys, angionecrotic nephrosclerosis.

## SUMMARY

1. One of a group of cases has been described in which the characteristic feature is endarteritis with necrosis of the vessel wall, and subsequent changes in the renal parenchyma.

2. The vascular changes are not restricted to the kidney, but are also found in vessels of the other organs of the body.

3. Clinically, these cases are characterized by a comparatively rapid development of renal insufficiency. Changes of the eyegrounds are conspicuous.

4. The condition is found in young or middle aged persons in contradistinction to cases described as arteriolosclerotic nephrosclerosis.

5. The following nomenclature is suggested: renal thrombo-angionecrosis for the more acute form and angionecrotic nephrosclerosis for cases of longer duration.

# TOXIC CIRRHOSIS OF LIVER DUE TO CINCHOPHEN *

HERBERT S. REICHLE, M.D.
CLEVELAND

Cinchophen is widely regarded as a drug of low toxicity. Sollmann [1] gave no warning against long continued massive doses, and the general practice is to maintain saturation over long periods. Graham [2] and others in England and Germany recommended that the drug be given for a period of about four days and discontinued for a similar interval. It is maintained that this procedure produces maximum beneficial effects without danger. My purpose in this paper is to report two fatal cases of cirrhosis of the liver apparently due to prolonged and massive administration of cinchophen.

In 1922, Schroeder [3] first drew attention to the toxic effects of cinchophen and published a review of seventeen cases. Since then twenty-eight cases have been found in the literature. In this country, Rabinowitz [4] and Sutton [5] have drawn attention to the toxicity of this drug. The principal symptoms are headache, gastro-intestinal disturbance and icterus.

There is little doubt but that natural idiosyncrasy may be of importance. Evans' [6] patient took only 15 grains (0.97 Gm.) of the drug. In other cases the amounts ranged from 80 to 4,000 grains (5.2 to 260 Gm.) over variable periods. The symptoms, as a rule, appear late in the course of treatment. It is also thought that idiosyncrasy may be artificially induced. Worster-Drought's [7] patient, after having taken 370 grains

* Submitted for publication, Feb. 15, 1929.

* From the Department of Pathology, Cleveland City Hospital and School of Medicine, Western Reserve University.

1. Sollmann, T.: A Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926.

2. Graham, G.: Presidential address, Section of Therapeutics and Pharmacology, Royal Society of Medicine, October, 1926; quoted from Loewenthal, Macay and Lowe: Brit. M. J. **1**:592, 1928.

3. Schroeder, K.: Cases of Cinchophen Poisoning, Ugesk. f. Laeger, **84**: 1141 (Sept. 7) 1922; quoted from Loewenthal, Macay and Lowe: Brit. M. J. **1**:592, 1928.

4. Rabinowitz, M. A.: Toxic Hepatitis and Hepatolysis Following Use of Atophan, M. Clin. N. Amer. **11**:1025, 1928.

5. Sutton, D.: Acute Yellow Atrophy of the Liver Following the Taking of Cinchophen, J. A. M. A. **91**:310 (Aug. 4) 1928.

6. Evans, G.: Discussion, Brit. M. J. **2**:689 (Oct. 16) 1926.

7. Worster-Drought, C.: Atophan Poisoning, Brit. M. J. **1**:148 (Jan. 27) 1923.

(25.05 Gm.) in twelve days, developed urticaria, which disappeared when the medication was stopped. One dose of 7½ grains administered three weeks subsequently brought on urticaria, gastro-intestinal disturbance and jaundice, which lasted ten days.

A dangerous aspect of cinchophen poisoning is the late and relatively abrupt onset of the symptoms. In the fatal case reported by Willcox,[8] the first signs of poisoning appeared at the completion of the treatment. In one of Loewenthal's[9] fatal cases jaundice developed two weeks after the medication had been stopped. Immediate reactions have been observed only on the intravenous use of the cinchophen derivative, diiodoatophan, containing about 50.7 per cent of iodine.

The most frequent symptom is jaundice. It developed in every case except those of Phillips[10] and Herrick,[11] which were very mild and showed only a rash. Vomiting, anorexia, heart burn and diarrhea, though not seen in every case, when present usually appear before the jaundice. The cinchophen rashes are either of the scarlatiniform type or are urticarial; there may also be petechial manifestations of the skin. In the later stages of the toxicosis the typical signs and symptoms of advanced destruction of the liver occur, namely, purpura, restlessness or coma, high icteric index, urobilin and tyrosin in the urine. The stools may be acholic. If the patient survives, cirrhotic changes occur which may lead to a diminution of liver volume and to an interference with the portal circulation. Damage to the kidney has been demonstrated clinically and is proved by the results of several autopsies. The clinical picture, therefore, is mainly one of serious damage of the liver, and it is probable that this accounts for all the symptoms, including the late skin rashes.

The seven autopsies that I have found recorded and those on my cases substantiate this hypothesis. In every case there was evidence of an "hepatitis" or of a degeneration of the parenchyma of the liver. Singer's[12] case showed only abundant round cell infiltration. The others all revealed more or less extreme fatty metamorphosis with or without periportal fibrosis. In same cases there was proliferation of the bile ducts. The livers were all small, with the exception of that in my first case, and ranged in weight from 500 to 1,150 Gm. A nephrosis,

8. Willcox, W. H.: Atophan Derivatives in Rheumatism, Brit. M. J. **2**:273 (Aug. 7) 1926.

9. Loewenthal, L. J. A.; Macay, W. A., and Lowe, E. C.: Two Cases of Yellow Atrophy of the Liver Following the Administration of Atophan, Brit. M. J. **1**:592 (April 7) 1928.

10. Phillips, J.: Skin Rashes Following the Administration of Atophan, J. A. M. A. **61**:1040 (Sept. 27) 1913.

11. Herrick, W. W.: A Scarlatiniform Rash from Atophan, J. A. M. A. **61**:1376 (Oct. 11) 1913.

12. Singer, S.: Discussion, Wien. klin. Wchnschr. **40**:238, 1927.

with damage particularly to the convoluted tubules, was noted in four cases.

Loewenthal [9] spoke of a subacute nephritis. Rake [13] mentioned hemorrhages in the suprarenal glands. There have been ten fatalities in the forty-six cases, and nine have come to autopsy. Two of the poisonings were due to the cinchophen derivative diiodoatophan. Twelve deaths are reported in Loewenthal's [9] survey, but I do not include them since he does not give the references.

## REPORT OF CASES

Case 1.—A white woman, aged 20, in January, 1928, developed an acute arthritis which affected almost all the joints. She was in bed for three months, and in May a tonsillectomy was done. One week following this operation, the patient became jaundiced and developed high fever and diarrhea. The gastrointestinal disturbances lasted six weeks. In June, the patient recovered and was able to walk about. A second attack of arthritis intervened which lasted up to the time of admission to the City Hospital. On Aug. 14, 1928, her physician found that she had an evening fever of 102 F. She was also suffering from severe nosebleeds and from hemorrhages around the gums. On August 19, she was admitted to a Cleveland hospital for various roentgen examinations and observations on the blood, which all proved negative. On September 9, the patient became worse. The temperature was 103 F. There was vomiting, diarrhea, pain in the right side of the chest and apathy. She was admitted to the City Hospital, Cleveland, on Sept. 13, 1928. She was emaciated and listless. The skin was dry and hot. There was a maculopapular eruption on the face, moderate pallor and hemorrhage from the nose and gums. The heart rate was 88, the blood pressure was 90 systolic and 52 diastolic, and the liver was palpable 3 or 4 cm. below the costal margin. The spleen was firm and easily felt. There was no evidence of bone or joint disease at that time. The urine contained a trace of albumin. The Wassermann reaction was negative. Examinations of the blood showed a severe anemia (2,080,000 red blood cells and 46 per cent hemoglobin, Sahli) and a rather high platelet count of 800,000. There were 12,240 leukocytes, of which 78 per cent were polymorphonuclears. The stool did not contain typhoid bacilli. Blood cultures were negative on two occasions. The Widal test was negative, and urine cultures gave no growth. The joints became swollen again; pneumonia developed. The temperature dropped to subnormal in the last two days, and the pulse rate rose to 120. The patient died on Sept. 18, 1928. The patient's first physician had given her cinchophen in January. The exact amount could not be ascertained but it is probable that she had at least as much as was given to her by her second physician, namely, 80 tablets of cinchophen of 7½ grains (4.87 Gm.) each and, in addition, 40 tablets of oxyiodide, which is a combination of iodine and cinchophen. In the City Hospital she had been given at least 60 grains (3.9 Gm.) of cinchophen.

At autopsy the body appeared poorly nourished. There were ecchymoses and petechiae beneath the skin. The skin was of a light lemon color. The heart was normal. There was confluent bronchopneumonia of the lower lobes of both lungs and the upper lobe of the right lung, which had progressed to abscess formation.

13. Rake, G. W.: A Case of Subacute Yellow Atrophy Following the Taking of Atophan, Guy's Hosp. Rep. **77**:229, 1927.

The liver weighed 1,950 Gm. and extended 4 cm. below the inferior costal margin. The capsular surface was uneven and showed projecting, irregular, firm, mustard yellow areas. With the knife a fatty fluid was expressed from the liver tissue. The bile ducts were patent. The spleen weighed 325 Gm. and was the seat of acute hyperplasia. The kidneys weighed 325 Gm.; in one there were several cortical abscesses. The cortices of both kidneys were distinctly yellow. Microscopic sections showed the following conditions: The cytoplasm of practically all of the liver cells was occupied by many vacuoles of varying sizes which sudan III fat stain showed to be fat. What was left of the cytoplasm was granular. The sinusoids were dilated. There was an enormous amount of connective tissue in the portal spaces which contained a large number of small round cells and some hemorrhage. Islands of liver tissue were cut off or entirely replaced by connective tissue. There was a definite proliferation of the bile ducts. Sudan

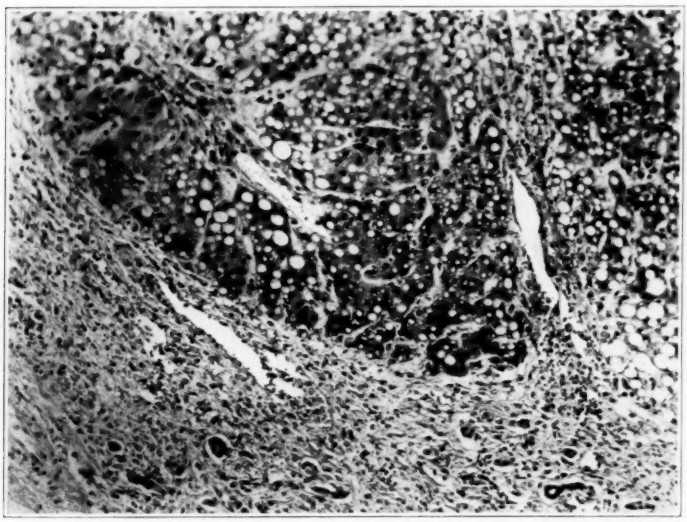

Fig. 1 (case 1).—Photomicrograph (100 diameters) showing fatty degeneration of liver cells and increase of connective tissue.

III fat stain showed an extensive accumulation of fat in the basal portions of the cells of the convoluted tubules of the kidney. Fat was also present but more diffusely in the epithelium of the collecting tubules. The epithelium of the tubules showed severe retrogressive changes which in part had led to a complete loss of cytoplasm and nuclei. Many of the collecting tubules contained nothing but fibrillar substance and a homogeneous pink-staining material. The subcapsular space of the glomeruli was occupied here and there by a pink granular material. One section showed a sharply defined necrosis of the parenchyma and interstitial tissue beneath the capsule. About this area there was a zone of fibroblast proliferation. The connective tissue was not increased elsewhere in the kidney. The heart showed no abnormalities.

Since the autopsy was done within eight hours of death, the observations on the kidney were of importance. The liver was examined for phosphorus by

Dr. H. H. Beard of the department of biochemistry of Western Reserve University. Mitscherlich's test showed that no phosphorus was present. The pathologic diagnosis, therefore, was: confluent bronchopneumonia of the lung with abscess formation, abscess of the kidney, fatty degeneration of the kidney, toxic cirrhosis of the liver and acute splenic hyperplasia.

CASE 2.—A white woman, aged 46, had been treated in the City Hospital Dispensary for arthritis over a period of three years. Cinchophen had relieved the pain, and the drug had therefore been repeatedly administered. The dose had been 15 grains (0.97 Gm.) from three to four times a day; over briefer periods of time 7½ grains had been given. In 1926, the total amount taken was 3,150 grains (204.75 Gm.); in 1927, 2,100 grains (136.50 Gm.), and in 1928 up to the onset of the fatal illness, 1,800 grains (117.40 Gm.). The Wassermann reaction of the blood was negative.

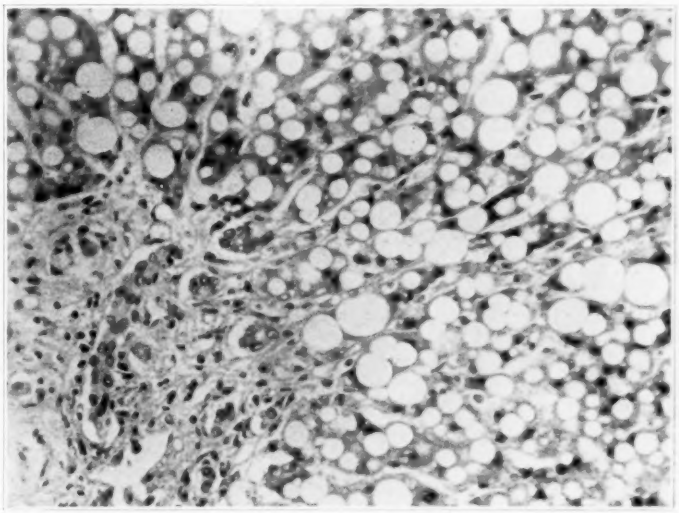

Fig. 2 (case 1).—Photomicrograph (200 diameters) showing fatty degeneration of liver cells, proliferation of bile ducts and young connective tissue.

On November 17, the patient returned to the Dispensary of the Cleveland City Hospital. For three weeks she had noticed that pain and tenderness in the epigastrium ("stomach trouble") followed the ingestion of the cinchophen. The dosage during this time had been 7½ grains four times daily. The patient felt weak and complained of "nervousness." The skin was icteric and showed a rash; the eyelids were puffy, and she had gained 6 pounds (2.7 Kg.) in about six weeks. The urine contained large quantities of bile pigment and a few casts. The temperature was normal.

The patient was admitted to the hospital on November 21. The epigastric pain had ceased, but the icterus was worse and nausea and vomiting had set in. She was confused, apprehensive and at times semicomatose. The admitting physician ascribed her mental condition to an injection (morphine?) which had been given by a private physician for the severe epigastric pain. However, the disorientation

and stupor increased. There were twitchings of the muscles of the arms and face, and on the sixth day generalized convulsions set in. The breath had an acetone odor, the spleen was not palpable and on percussion the liver dulness was found high above the costal margin. The Babinski and Oppenheim reflexes and ankle clonus were present bilaterally. The temperature rose to 39 C. (102.2 F.), and the patient died in coma with the signs and symptoms of pulmonary edema on the sixth day of her hospital stay.

The total urinary output was never more than 300 cc., and the urine was strongly positive for bile and contained granular casts, white blood cells and albumin. On the day of admission, the chemical examination of the blood gave the following results: sugar, 108 mg. per hundred cubic centimeters; carbon dioxide (saturation volume), 27 per cent; whole blood chlorides, 474 mg. per hundred cubic centimeters, and urea nitrogen, 27 mg. per hundred cubic centi-

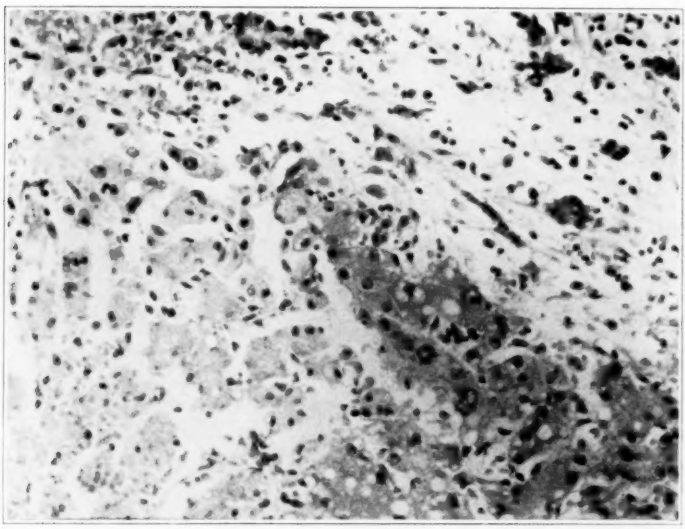

Fig. 3 (case 2).—Photomicrograph (300 diameters) showing fatty degeneration and hyalinization of liver cells, proliferation of bile ducts and increase in connective tissue.

meters. The next day the icteric index was determined and found to be 80. On the third day, the plasma chlorides were 563 mg. per hundred cubic centimeters, and the carbon dioxide saturation volume was 37 per cent. On November 23, the white blood cell count was 11,000; the hemoglobin (Sahli), 85 per cent.

Autopsy was done four hours after death. The body was obese and very icteric, and the skin showed a papular eruption over the chest and extremities. Petechiae were found on the skin and in the mucous and serous membranes. The liver weighed only 575 Gm. Its surface was nodular; individual yellow nodules, which were about 1 mm. in diameter, were separated by a red, firm tissue. On cut section, irregularly formed islands of soft yellow tissue were found in a mass of red and firmer tissue. The gallbladder contained a normal amount of thin bile and a few cholesterol stones. The two kidneys together weighed 400

Gm. They were pale and the surface was smooth; on cut section, the tissue bulged and the normal architecture was indistinct. The pyramids were streaked with yellow. There was an increase in peripelvic fat. The stomach contained a coffee-ground material, and the mucosa of the entire gastro-intestinal tract was hyperemic.

The histologic observations were as follows: The myocardial fibers stained poorly. A fat stain (sudan III) revealed an extensive fatty degeneration of the muscle fibers. The epithelium of the tubules of the kidney was swollen and granular. Sudan III stain showed the presence of an enormous amount of intracellular fat. Here and there in the liver a few islands of liver tissue were found in a mass of young connective tissue which was infiltrated by many small round cells. The bile ducts had proliferated to a remarkable degree. The liver tissue

Fig. 4 (case 2).—Photograph of liver to show the size (scale in inches) and nodular surface.

that was left was in a state of cloudy swelling, vacuolization or hyalinization. Hardly one normal cell could be found. There was extensive hemorrhage into the masses of necrotic cells. The sudan III stain demonstrated free fat in all these cells. The rest of the organs, spleen, pancreas, lung and uterus, showed chronic passive hyperemia.

The pathologic diagnosis, therefore, was: toxic cirrhosis of the liver, fatty degeneration of the myocardium and kidney, and passive hyperemia of all organs.

It is probable that there are many more cases of toxemia due to cinchophen than one is aware of. At a conference in the City Hospital at which one of my cases was presented, several physicians reported that they had seen jaundice during the period of medication with

cinchophen. The first sign of gastro-intestinal disturbance should therefore be an indication for stopping the drug. Jaundice must be regarded as a symptom of serious damage to the liver. The cases of Willcox [8] and Loewenthal [9] in which no legitimate precaution had been neglected raise the question as to whether or not the use of cinchophen is of such great value that it warrants the danger. Willcox's patient had had only 85 grains (5.52 Gm.); Loewenthal's patient had been treated according to the Graham method. In both cases the symptoms set in after the medication had already ceased. The experience of those who have used the cinchophen derivative, diiodoatophan, proves that cinchophen given in one large dose may produce the same damage as when given in smaller doses over long periods of time. The number of cases already reported is sufficiently great to eliminate the probability of mere coincidence.

## CONCLUSION

Forty-seven cases of cinchophen toxicosis have been published.[14] Ten deaths have resulted. In all cases there is evidence of serious damage of the liver. Every patient who receives cinchophen should be observed for gastro-intestinal symptoms, rashes or icterus and the occurrence of such symptoms should be the immediate indication for stopping the use of the drug. The therapeutic use of cinchophen may well be reevaluated in reference to its harmful properties.

I am indebted to Dr. Howard T. Karsner for taking the photomicrographs which illustrate this article.

14. De Rezende recently published a case (Brasil-med. **41**:1005 [Sept. 24] 1927), and Motzfeldt described a case of icterus due to cinchophen, Norsk. Mag. f. Laegevidensk., March 21, 1929, p. 283.

# THE PNEUMOTACHOGRAPH IN CERTAIN INTRATHORACIC DISEASES

## ITS DIAGNOSTIC VALUE *

MAX HOCHREIN, M.D.
AND
SOMA WEISS, M.D.
BOSTON

### INTRODUCTION

The close functional and anatomic relationship between the heart and lungs is well recognized. Disturbance in the normal functions of the lungs may have considerable importance in diseases of the heart and blood vessels. Occasionally, respiratory changes are the first recognizable signs of circulatory failure. It is partly for this reason that, in the past, the respiration has been studied carefully with the aid of a number of technical devices. The excursions of various parts of the thoracic wall have been registered. Similarly, volumetric measurements of the ventilation have received careful consideration. Through the earlier investigations of Bergeon and Kastus,[1] Rosenthal,[2] Gad,[3] Ewald[4] and Gevers-Leuven,[5] and through the more recent studies of Pech[6] and Beyne,[7] it has become an established fact that the velocity of the respired air is also of considerable importance in the mechanism of the respiration. Recently, Fleisch[8] described an apparatus which registers the

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* From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, and the Department of Medicine, University of Leipzig, Germany.

1. Bergeon, L., and Kastus, C.: Nouvel appareil enregisteur de la respiration, Gaz. hebd. de méd., 1868, vol. 579.

2. Rosenthal, J.: Die Physiologie der Atembewegungen, in Hermann: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, vol. 4, chap. 2, p. 223.

3. Gad: Einige kritische Bemerkungen die Pneumotachographie betreffend, Arch. f. Anat. u. Physiol. **2**:553, 1879.

4. Ewald, I. R.: Der normale Atmungsdruck und seine Kurve, Arch. f. d. ges. Physiol. **19**:461, 1879.

5. Gevers-Leuven: Contribution à l'aorodynamique des voies respiratoires, Untersuchungen aus dem physiologischen Laboratorium, Utrecht, 1904.

6. Pech, S. L.: La notion du debit respiratoire maximum, mésure pratique de ce debit au mogen du moyen manométrique, Presse méd. **29**:93, 1921.

7. Beyne, J.: L'étude graphique du debit respiratoire au moyen du masque de Pech, Presse méd. **31**:698, 1923.

8. Fleisch, A.: Der Pneumotachograph; ein Apparat zur Geschwindigkeitsregistrierung der Atemluft, Arch. f. d. ges. Physiol. **209**:713, 1925.

velocity curve of the inspired and expired air. The velocity curve is an expression of the differential quotient of the respiratory volume over time. Fleisch's pneumotachograph consists of ninety tubes, each 20 cm. long and 2 cm. in diameter. The resistance offered by the tubes when the subject is breathing through the mouth piece, and the fall in pressure between the two ends of the tubes, are functions of the velocity of the respired air. Although the resistance offered the tubes of the apparatus is not sufficient to cause an alteration of normal respiratory movements, the dead space is rather undesirable.

## APPARATUS

The pneumotachograph used in this study has been described by one of us.[9] The instrument is based on the following principle: If a fluid or gas flows through a tube, the diameter of which changes suddenly from narrow to wide, the stream does not fill the first portion of the wider tube instantly; the pressure may be considerably lower here than in the narrower portion of the tube. If a small ring is fitted within a cylindric tube, during the passage of the air through the tube there is a difference in pressure between the two sides of the ring. This difference in pressure may be expressed in the following formula:

$$h = \frac{U^2}{2g}\left(\frac{F_2}{F_1} - 1 + \frac{1}{3}\right)$$

if $h$ represents the difference in pressure, $U$ the velocity of flow of the air, $g$ the gravity of the earth, $F_1$ the diameter of the inserted resistance, $F_2$ the diameter of the tube and $J$ the coefficient which is determined empirically. According to this formula, the difference in pressure is proportional to the velocity of the flow of air and to the degree of resistance. This principle receives, then, the following practical application in the apparatus:

In the middle portion of a metal tube, 5 cm. long, a ring is placed. The relation between the width of the ring and the diameter of the tube is 1:7. The ring inserted offers a resistance to the stream of air entering into the metal tube; a difference in pressure is therefore created between the two sides of the ring. This difference in pressure is proportional to the velocity of the stream of air. Therefore, if this difference in pressure is registered with a differential capsule, which is then empirically calibrated to a number of currents of gas of known velocity, the curve obtained gives a direct measure of the velocity of the current of air. For the registration of the differences in pressure, a sensitive modified Frank differential capsule is used. A small mirror attached to the membrane reflects a small narrow beam of light on a moving film. The connection between the respiratory tube $R$ (fig. 1) and the differential capsule $D$ (fig. 1) is established with two short rubber tubes, $A_1$ and $A_2$ (fig. 1). The distance from the opening of these tubes into the respiratory tube to the metal ring inserted into the tube is equal on both sides. For quantitative calibration, the apparatus is inserted between a gas tank and a gasometer, and standard curves are obtained with streams of gas of known velocity.

9. Hochrein, M.: Ueber Pneumotachographie, Arch. f. d. ges. Physiol. **219:** 753, 1928.

The curves obtained with the apparatus represent the differential quotient between the time and volume of respiration. If the curve is represented on cartesian coordinates, the abscissa of which represents the time, and the ordinate the velocity of the respired air, the volume of respiration can be obtained if the surface area that is enclosed by the curve and abscissa is measured with a planimeter. Preliminary heating of the respired air, required when the Fleisch apparatus is applied, is not necessary. The resistance of the apparatus is minimal, and the dead space is small, owing to the fact that the respiratory tube is short. The apparatus can be used in experiments on animals; in that case a small respiratory tube is inserted into the trachea.

The apparatus thus enables one to measure simultaneously: (*a*) the duration of inspiration and expiration; (*b*) the maximal, minimal

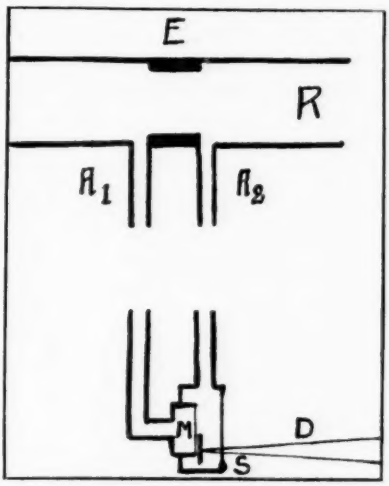


Fig. 1.—Diagram of the pneumatograph used. *R* is the respiratory tube, *D* the differential capsule, *E* the narrow portion of the tube, *M* the Frank capsule, *S* light to mirror.

and mean velocity of the expired air; (*c*) the volume of a single respiration; (*d*) the rate of respiration, and (*e*) the respiratory minute volume.

Figure 2 represents the pneumotachogram (*P*) of a normal subject, with the simultaneously registered heart sounds (*S*), electrocardiogram (*E*) and velocity curves for the pulse (*V*). In analyzing the pneumotachograms of normal persons, one finds that there are small irregularities superimposed on the inspiratory and expiratory curves. These irregularities have been noted by previous investigators. Fleisch[5] attributed them to fluctuation in the velocity of respired air, as a result of uneven function of the respiratory muscles. That at least some of the fluctuations in the velocity do not depend on the function of the respiratory muscles, but have a relationship to the cardiac function, can

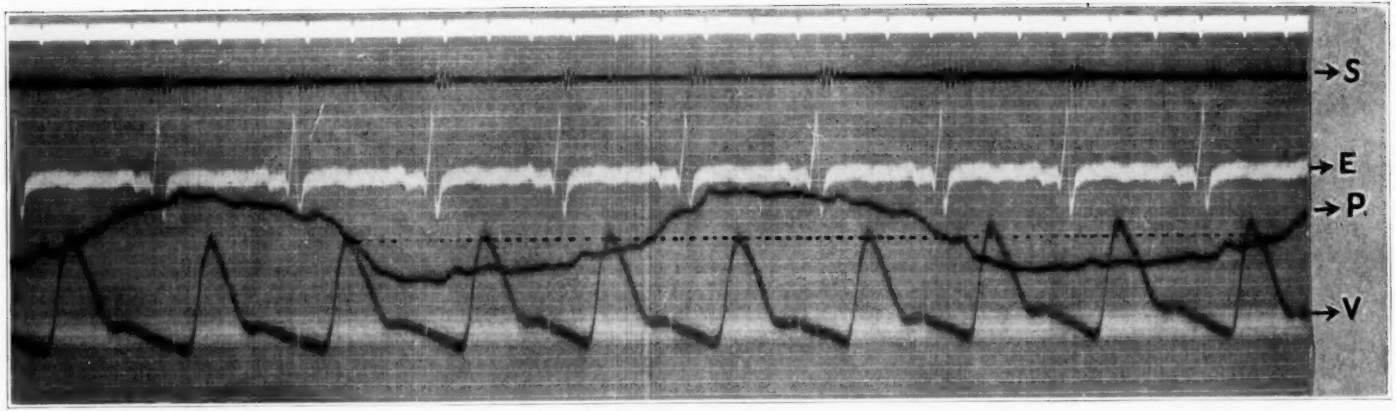


Fig. 2.—Pneumotachogram (*P*) of a normal subject with simultaneously registered heart sounds (*S*), electrocardiogram (*E*) and velocity curves of the pulse (*V*).

be demonstrated if one simultaneously registers the heart sounds or cardiac action (electrocardiogram) with the pneumotachogram. If the respiration stops, the pneumotachogram continues as a straight line, in normal persons, and no notches are observed.

In extending our observations from normal subjects to patients with cardiovascular and pulmonary diseases, it was found that some of the patients showed notchings of the pneumotachograms even during respiratory standstill. These notchings were present in inspiratory standstill only in some of the patients observed, and in both inspiratory and expiratory standstill in others. It was also observed that certain simple respiratory gymnastics intensified or decreased these notchings of the curves. It was our aim, therefore, to determine the mechanisms and the significance of the presence and absence of these notchings of the pneumotachograms.

## EXPERIMENTAL OBSERVATIONS

After a number of attempts, the following experiment was performed on normal subjects and on patients studied: The pneumotachogram and electrocardiogram, or the heart sounds, were registered simultaneously during the natural state of the respiration. Then the subject took a deep inspiration, followed by a respiratory standstill of six seconds' duration; a forcible expiration followed, with another respiratory standstill of six seconds' duration at the end of the expiration. In registering the normal respiration and the described respiratory gymnastic of fifty normal subjects, no definite notchings synchronous with the heart action during the respiratory standstill were observed. The tracing continued as a straight line during respiratory standstill.

Figure 3 represents such an observation, with simultaneously registered heart sounds, electrocardiogram and velocity curve of the pulse. With the onset of respiratory standstill at the end of a forceful inspiration, the tracing falls to the zero line and forms a straight line until the respiration is resumed. Occasionally, irregularities occur during the respiratory standstill. These, however, have no relation to the function of the heart, and are due either to swallowing movements or to the fact that a number of elderly persons are unable to hold their breath completely; even if the extrathoracic muscles stop their activity, slight excursions of the diaphragm continue. It is also important that during the respiratory standstill the vocal cords should be kept open, for if closed, the pneumotachogram will always show a straight line.

The eighty-three patients whose respirations were studied had the following conditions: valvular disease of the heart, (*a*) ten cases of syphilitic origin and (*b*) twenty-five cases resulting from rheumatic fever; syphilitic aneurysm of the aorta, six cases; arterial hypertension with myocardial hypertrophy, twenty-one cases; adhesive pericarditis, four cases; tumors of the lungs and of the pleura, seven cases, and other

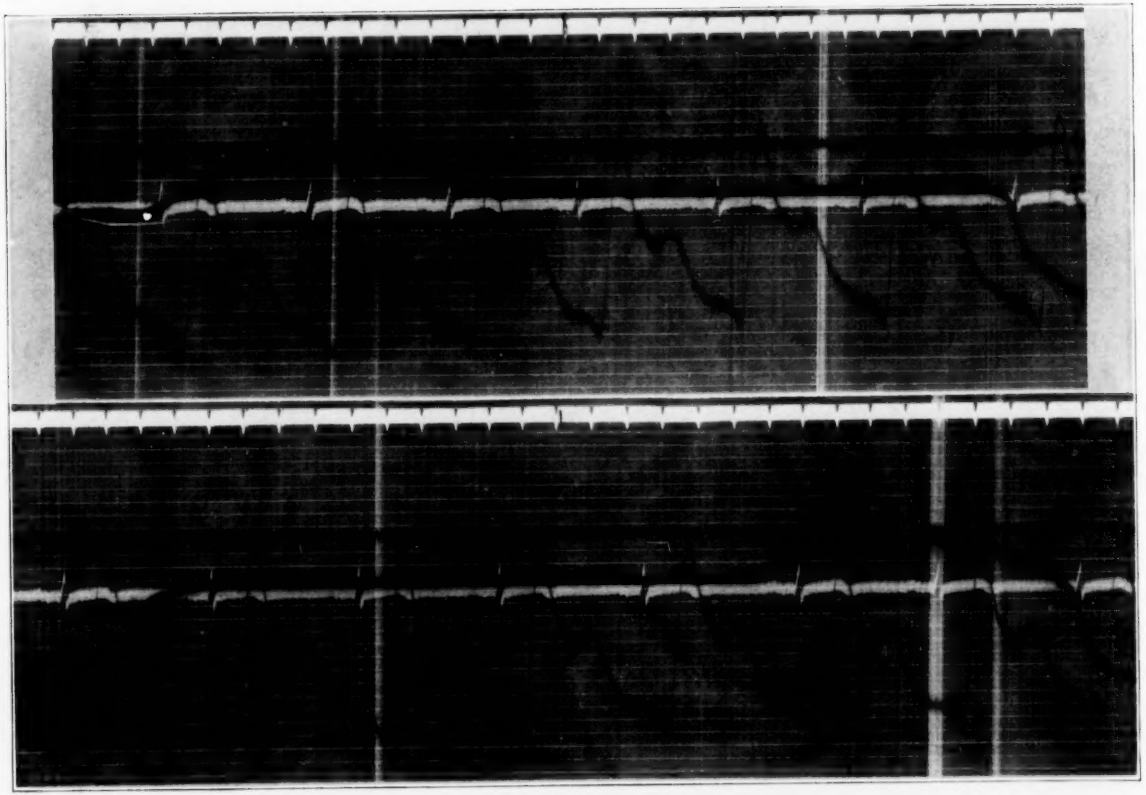

Fig. 3.—Pneumotachogram of a normal subject during forced inspiratory and expiratory standstill, with simultaneously registered heart sounds, electrocardiogram and velocity curves of the pulse. The upper and lower tracings form a continuous record.

disorders of the lungs, ten cases. The majority of the patients observed had respiratory curves which were identical with those of normal subjects. The pneumotachograph of patients with circulatory failure, as expected, showed an increased respiratory rate, and occasionally increased minute volume. Similarly, the tracings of the majority of the patients gave a straight line during the respiratory standstill. In six patients, however, with aneurysm of the thoracic portion of the aorta, notchlike elevations synchronous with the heart action were observed during both the inspiratory and the expiratory standstill, although the notchlike elevations were more marked in inspiration. An analysis of the notching in its relation to the heart sounds indicated that with cardiac systole a small amount of air is expelled from the lungs; synchronously with the second sound, which corresponds to the closure of the aortic valves, a small amount of air flows back into the lungs although the respiratory muscles are not active.

The phenomena observed, in our opinion, are best explained by recalling that thoracic aneurysms of the aorta are usually in close contact with the pleural surface. Firm adhesions between the wall of the aneurysm and pleura are often observed. The aneurysmal sac of the arota, therefore, may act as a pressure and suction pump and may produce fluctuations in the content of air in the lungs, which is registered with the sensitive apparatus applied. We observed, altogether, six patients in whom the diagnosis of syphilitic aneurysm was established by clinical evidence, serologic observations and fluoroscopic and roentgen examinations. If observations on a larger number of patients with aneurysm indicate that this notching of the pneumotachogram is present in a high percentage of such patients, the sign should be considered an important and valuable aid in the diagnosis of aneurysm of the aorta.

Following the observations on patients with aneurysm of the thoracic portion of the aorta, studies were made of the inspiratory mechanism of patients with tumors of the lung and pleura. As is well recognized, the differential diagnosis between aneurysm of the aorta and neoplasms located in the mediastinum is occasionally most difficult and sometimes impossible. All the signs of differential diagnostic importance may be present in both conditions. The roentgen shadow of a solid tumor and of a pulsating aneurysm may be identical. It is true that an irregularly outlined shadow favors the presence of tumor, but multilocular aneurysms are not rare. Under fluoroscopic examination, both tumors of the lungs and those of the pleura may show transmitted pulsations which are synchronous with the heart. A shadow which extends into the lung field favors the diagnosis of tumor of the lung, as it is most frequently associated with bronchial carcinoma. This sign, however, may be absent in the case of malignant tumors, and may

Registered heart sounds, electrocardiogram and velocity curves of the pulse. The upper and lower tracings form a continuous record.

be present as a complication in aneurysm. Aneurysms of the arch of the aorta are especially likely to produce compression of the left bronchus which may result in partial or complete atelectasis of certain areas of the lung. Such a clinical condition may give a roentgen and fluoroscopic picture identical with that of a tumor of the lung. Paresis of the recurrent laryngeal nerve and compression of the vena cava may also occur in both conditions. Similarly, hemoptysis may develop in such conditions. Effusions in the pleural cavity may be present both in patients with tumor of the lung and in patients with aneurysm. The practical significance of this differential diagnostic problem has grown during recent years, as the frequency of primary malignant tumors of the lungs has increased considerably both in America and in Europe during the past few years.

We studied the respiratory mechanism of seven patients in whom the diagnosis of tumor of the lung was established by autopsy or by the appearance of metastasis during life. The respiratory curves of all seven cases observed were identical with those of normal subjects. The characteristic notches seen in the pneumotachograms of patients with aortic aneurysms were not observed. Figure 4 represents the pneumotachogram of a patient with aneurysm and of one with tumor of the lung, verified by postmortem examination.

Considering that aneurysm, like mediastinal tumor and tumor of the lung, is relatively rare, the observations on six patients with aneurysm and on seven patients with tumor of the lung are sufficiently large to attach significance to these observations. The possibility that certain aneurysms may not give the sign, and that some mediastinal tumors may produce notchings of the pneumotachogram during respiratory standstill, can be ruled out definitely only after a study of a larger number of cases. Repetition of the observations, therefore, will facilitate settling that aspect of the problem.

In addition to the patients with aneurysm of the thoracic aorta, patients with clinical signs of adhesive pericarditis exhibited notchings synchronous with the heart beat during inspiratory standstill, but, in contrast to the patients with aneurysm, they failed to show notchings during the expiratory standstill. Figure 5 is a tracing obtained on a patient with adhesive pericarditis.

Our interpretation of the pneumotachograms of patients with adhesive pericarditis is as follows: It is recognized that in a number of patients with adhesive pericarditis, firm adhesions are present not only between the visceral and parietal layers of the pericardium (accretio), but also between the parietal pericardium and pleura (concretio). This latter type of adhesion may be intense enough over the diaphragmatic aspect of the pleura to exert a pull on the diaphragm, which, in turn, produces a visible pulsation over its place of attachment. This can be

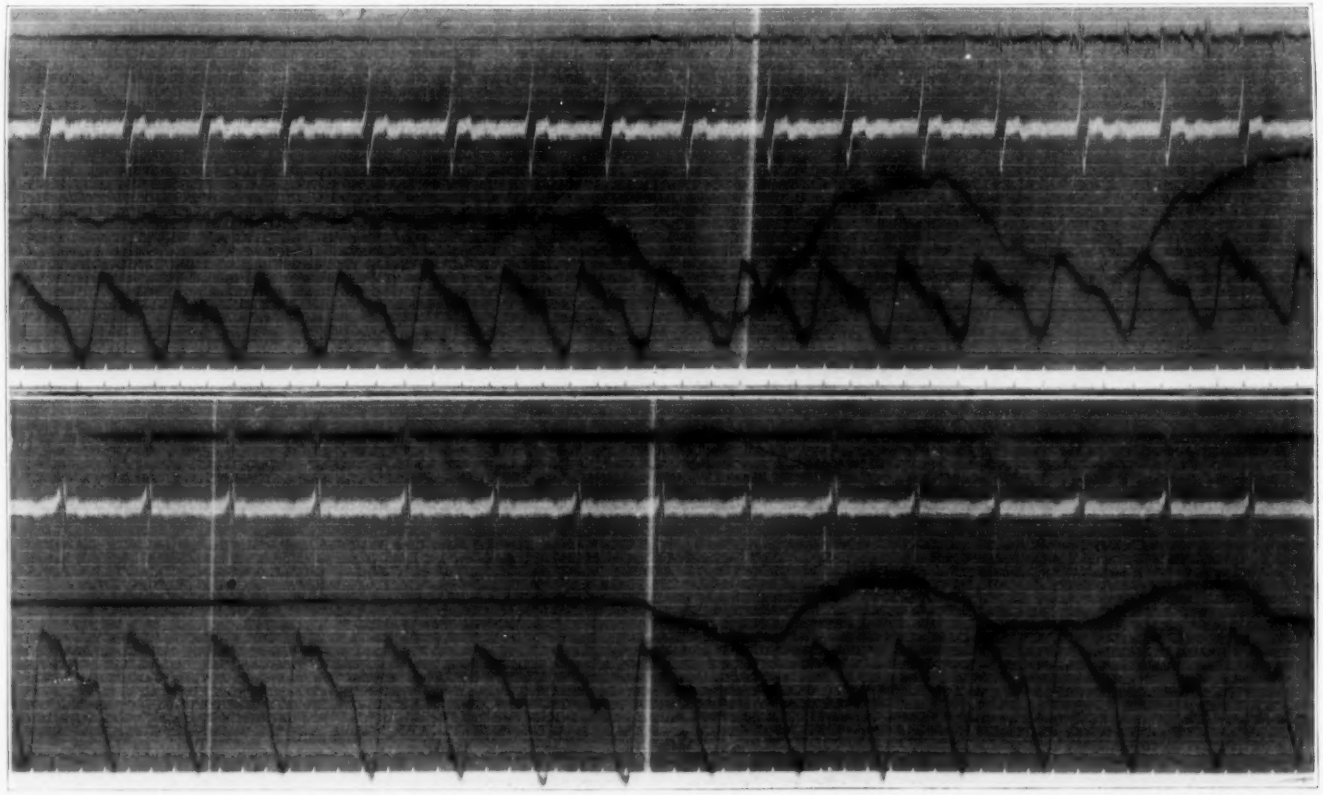

Fig. 4.—Pneumotachograms of natural breathing followed by inspiratory standstill in a patient with primary carcinoma of the bronchus of the right lung (upper tracing), and that in a patient with aneurysm of the arch of the aorta (lower tracing).

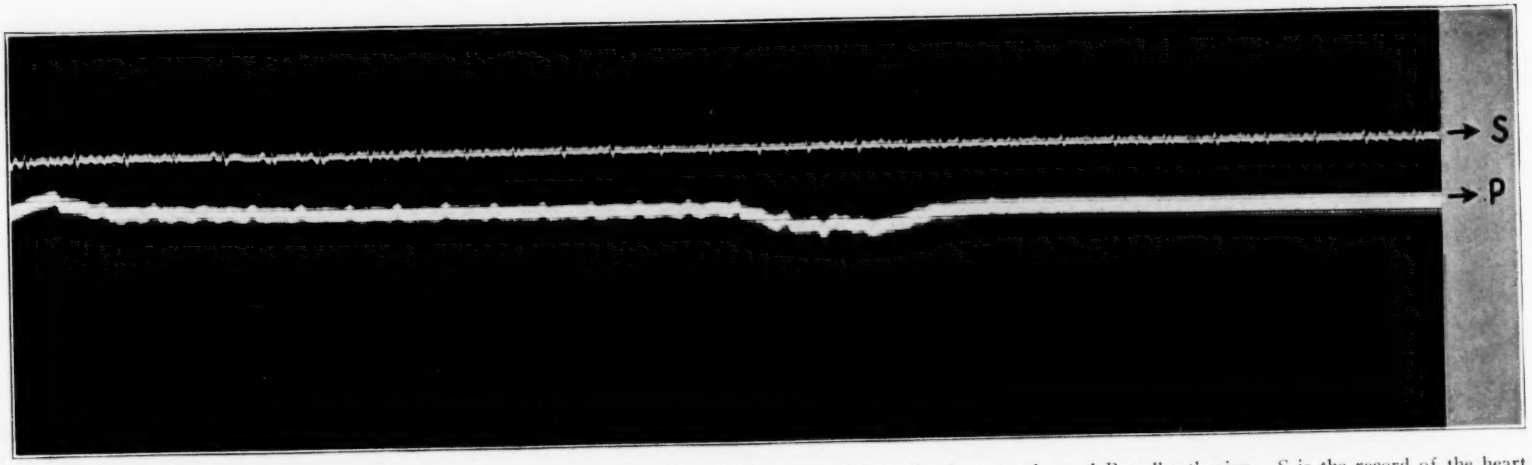


Fig. 5.—Pneumotachogram of a patient who had chronic rheumatic endocarditis with marked cardiac hypertrophy and Broadbent's sign. *S* is the record of the heart sounds; *P* is the pneumotachogram during inspiratory and expiratory standstill.

observed easily near the region of the floating ribs (Broadbent's sign). This sign is present only in a relatively small percentage of patients with adhesive pericarditis. It is our contention that the behavior of the pneumotachogram in adhesive pericarditis depends on identical pathologic changes, with the result that during inspiration when the diaphragm is lowered and the pull of the adhesions is increased, a pulsating movement of the diaphragm will occur which in turn causes a to-and-fro fluctuation of air in the lungs, provided there is a free communication with the outside air. During expiration, the adhesions being looser, the pull exerted is insufficient to produce pulsating movements of the diaphragm.

Special importance is attached to the fact that in addition to the cases with definite clinical and laboratory observations indicating the presence of adhesive pericarditis, seven of twenty-five patients, or 28 per cent, with chronic rheumatic endocarditis but no signs of adhesive pericarditis showed the same phenomena. We believe that the mechanism of the notchings of the respiratory curves in these patients is identical with that observed in patients with clinical manifestations of pericarditis. It is recognized that adhesive pericarditis occurs in rheumatic disease of the heart more frequently than one may judge from the clinical behavior of the patients. This conception is substantiated by a comparison of the clinical behavior of patients in the Boston City Hospital, who died and in whom the postmortem examination revealed pathologic changes of the mitral aspect of the endocardium characteristic of chronic rheumatic endocarditis. An analysis showed that in seventeen of sixty-three cases (27 per cent) of mitral disease, marked adhesions of the pericardium were present although, clinically, in only three instances was adhesive pericarditis suggested.

The presence of notchings in the pneumotachograph during inspiratory standstill in a number of patients with chronic rheumatic endocarditis, therefore, may be the only sign indicative of the presence of adhesive pericarditis.

## SUMMARY AND CONCLUSIONS

1. The velocity of the respiration during its natural state and during certain respiratory gymnastics was studied in fifty normal subjects and in eighty-three patients with diseases of the heart and lungs.

2. During inspiratory or expiratory standstill, the pneumotachogram of the normal subjects and of the majority of the patients is a straight line.

3. In six patients with aneurysm of the thoracic portion of the aorta, notchings of the pneumotachogram were observed during both inspiratory and expiratory standstill.

4. The pneumotachogram of four patients with clinical evidence of adhesive pericarditis and of seven of twenty-five patients with chronic

rheumatic endocarditis exhibited similar notchings during inspiratory standstill, but the tracing was a straight line during expiratory standstill.

5. Registration of the respiration with the pneumotachograph may be of considerable aid in certain diagnostic problems of intrathoracic pathology.

6. The observations indicate that under certain pathologic conditions the lungs act as sensitive plethysmographs for recording abnormal changes in the cardiac function.

# Book Reviews

PRAKTISCHE DIFFERENTIALDIAGNOSTIK FÜR AERZTE UND STUDIERENDE. VI. HAUT- UND GESCHLECHTSKRANHEITEN. I. HAUTKRANKHEITEN. By PAUL TACHAU, Physician for Skin and Venereal Diseases in Wolfenbüttel-Braunschweig. Price, 14 marks. Pp. 237, with 3 illustrations. Dresden: Theodor Steinkopff, 1929.

This volume is a concise but detailed work dealing with diagnosis and differential diagnosis of dermatoses.

Pages 5 to 38 include general considerations of primary and secondary lesions. On pages 39 to 142 the monomorphous diseases are considered, and on pages 143 to 197 the polymorphous diseases are dealt with. Diseases of the scalp occupy pages 198 to 207, diseases of the nails 207 to 210 and diseases of the mucous membranes 210 to 222.

The difficulties in the physical diagnosis of dermatoses make the work of less value to the practitioner who has had no special training in dermatology. This defect could have been partially remedied by photographic illustrations of various primary and secondary lesions. Since dermatologic diagnosis is governed largely by visual impressions, lack of illustrations is a serious fault. The text, however, is valuable in connection with advanced training of persons already founded in fundamental diagnosis.

The text is illustrated by three microscopic sketches, although other illustrations are said to form a supplement to the complete volume.

An excellent index occupies the last fifteen pages.

DIABETES LATENTE. By DR. FELIX PUCHULU. Buenos Aires: Ferrari Hnos, 1929.

This is the inaugural dissertation of one of the assistants in Escudero's Clinic, and consists of an admirable summary of the work done by the author, his chief and many others on the peculiar manifestations of diabetes in the preglycosuric stage.

It is claimed that in normal persons the ingestion of dextrose causes a rise in the blood sugar, followed later by a considerable fall below the point where the test began. This secondary fall is caused by the fact that the carbohydrate-storing mechanism has been speeded up. Failure of the occurrence of this fall is interpreted as a deficiency in carbohydrate metabolism and is looked on as a precursor of diabetes.

Such a condition was discovered in a series of sixty-one persons suffering from skin and ocular diseases of various types. When they were subjected to anti-diabetic therapy a marked improvement resulted.

THE PRINCIPLES OF CLINICAL PATHOLOGY IN PRACTICE. By GEOFFREY BOURNE and KENNETH STONE. Price, $4.75. New York: Oxford University Press, 1929.

Bourne and Stone's compendium suffers from the same ailment that has afflicted medical books in the past and that will afflict many in the future. The ambition of the authors and the range of the subject has impelled a cursory survey of many diseases; the limitation of the size of the book has resulted in a general superficiality. As a result, the product is in general unsatisfactory. Perhaps a conscious effort to write it down to the supposed level of the practitioner may have something to do with the obviously elementary character. Of the 370 odd pages, only 7 are devoted to the stomach, and none of the recent methods of analysis are even mentioned. The roentgen rays play no apparent rôle, and of modern chemical analysis of the blood there is hardly a suggestion. The book offers nothing of value to the modern practitioner.

CARDIAC ARRHYTHMIAS. By IRVING R. ROTH. Price, $7.50. Pp. 210. New York: Paul B. Hoeber, 1928.

The book is written in two sections, the first dealing with the anatomy and physiology of the heart and the second with the cardiac arrhythmias. The reading matter is reduced to a minimum, and diagrams and graphs are used to good advantage in explaining the interrelations of the various clinical phenomena in the normal as well as in the irregular heart beat. The book is especially attractive to the average practitioner and student. It is written clearly and briefly and is illustrated in an enlightening manner.

DAS EXSICCOSEPROBLEM. By PROFESSOR DR. ERWIN SCHIFF. Price, 6.80 marks. Pp. 85. Berlin: Julius Springer, 1929.

This is an excellent monograph on the subject of water loss by a pioneer worker in this field. Schiff considers the ways in which desiccation of the body is brought about. He discusses the pathologic, chemical and physical changes produced as a result of desiccation. The treatment of desiccation due to various causes is outlined. The bibliography is remarkably complete and includes references to more than 300 articles.

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